The Journal of
CLINICAL
ENDOCRINOLOGY

VOLUME 4 MAY, 1944 NUMBER 5
Copyright 1944 by the Association for the Study of Internal Secretions

Thiourea and Thiouracil in Treatment of Thyrotoxicosis[1]

K. E. PASCHKIS, M.D.,[2] A. CANTAROW, M.D.,
A. E. RAKOFF, M.D., A. A. WALKLING, M.D.,
AND W. J. TOURISH, M.D.

From The Jefferson Medical College and Hospital and the Pennsylvania Hospital, Philadelphia, Pennsylvania

SULFONAMIDES, thiourea and a number of other compounds have been found to suppress thyroid activity in experimental animals (1, 2). These drugs act by suppressing formation of thyroxin (1–5). Astwood, after a study of about 120 compounds (6), used two—thiourea and thiouracil—for treatment of patients with thyrotoxicosis (7). Williams and Bissell (8) have reported nine cases treated with thiouracil; Himsworth (9) has reported six cases treated with thiourea.

We are reporting here our experience with the use of thiourea and thiouracil[3] in 21 patients with thyrotoxicosis.

MATERIAL

The pertinent clinical data are summarized in the accompanying table.

RESULTS OF TREATMENT

Results were gauged by general clinical improvement—disappearance of nervousness, vasomotor instability, tremor and sweating, by return of pulse rate and BMR to normal values, and by weight increase. The serum cholesterol value was determined in the majority of cases. All patients responded favorably with the exception of *Case 2*, in which treatment with thiourea was discontinued after 6 days because of toxic manifestations (see below). Thiouracil was not available to us at that time. Full recovery, including return of the BMR to normal values, required two to three weeks of treatment but improvement was first noticeable usually after five to ten days. Noteworthy ex-

[1] To be presented before the Twenty-Seventh Annual Meeting of the Association for the Study of Internal Secretions, Chicago, Illinois, June 12, 1944.

[2] J. Ewing Mears Teaching and Research Fellow in Physiology and Medicine.

[3] The thiouracil used in this study was supplied by the Lederle Laboratories, Inc., through the courtesy of Dr. B. Carey.

Case No., Age, Sex	Type	Duration of symptoms prior to treatment	BMR before treatment	Interval of treatment before improvement	Drug and effective dose	Additional treatment	Surgical Procedures	Toxic Manifestations	Remarks
1. S.K. female, 26	Diffuse Slight ex.	6 months	55	14 days	2 gm. thiourea	Sedation; Bed-rest	None	Rash	
					1 gm. thiouracil (at times 2 gm.)	None	None	Rask, leukopenia after 8 months	
2. C.H. female, 23	Diffuse Slight ex.	Gradual; 4 years	50	—	2 gm. thiourea	Sedation; Bed-rest	Thiourea stopped. Op. after iodine prep.	Rash, vomiting	
3. J.H. female, 20	Diffuse Slight ex.	6 months	40	5 days beginning; 3 weeks marked	1 gm. thiouracil	Bed-rest	None	None	
4. E.P. female, 34	Diffuse	1 year	(27) 9	Gradual over 4 weeks	2.0 gm thiourea then 1 gm. thiouracil	Sedation; bed-rest. Pretreated with iodine	None	None	See text
5. M.C. female, 50	Diffuse	6 months	36	Gradual over 1 month	1 gm. thiouracil	None	None	None	See text
6. C.H. female, 31	Diffuse	3 months	45	14 days	1 gm. thiouracil	Bed-rest. Pretreated with iodine for 2 months without effect. Lugol Min. V t.i.d. continued during thiouracil treatment	None	None	Died of acute meningococcal septicemia
7. C.G. male, 49	Diffuse Exophth.	6 months	57	None during 4 weeks on 1 gm.; 9 days on 2 gm.	2 gm. thiouracil	Bed-rest during 1 gm. period; None while on 2 gm.	None	None	
8. C.G. female, 54	Nodular	Several years	30–40	14 days	1 gm. thiouracil	Bed-rest;	None	None	
9. M.B. male, 41	Diffuse	3 months	45–55	8 days	1 gm. thiouracil	Bed-rest	None	None	
10. R.S. male, 50	Diffuse	4 months	30–40	11 days	1 gm. thiouracil	Bed-rest; Sedation	Recurrence. Op. 3 years ago	None	
11. W.M. male, 34	Diffuse	1½ years	32	2½ weeks	1 gm. thiourea	None	Op. one year ago. Reoperated. Residual thyrotoxicosis. Refused further operation.	Gastrointestinal upset, perhaps due to thiourea	See text
12. A.N. female, 49	Diffuse	3 months	50–60	1 gm. for 2 weeks ineffective; 2 gm effective after 1 week	2 gm. thiouracil	Bed-rest; Sedation	Subtotal thyroidect.	None	Thiouracil used as preop. treatment
13. A.V. female, 50	Nodular	Several years	20	11 days	1 gm. thiouracil	Bed-rest	None	None	
14. M.H. female, 38	Diffuse Slight ex.	4 years	30–40	Moderate effect thiourea 14 days; Thiouracil 1 gm. 20 days	2 gm. thiourea	Bed-rest	None	Fever	
					0.8 gm. thiouracil	None	None	None	Temporary myxedema
15. M.S. female, 42	Diffuse Ex.	1 year	46	10 days	2 gm. thiourea	Bed-rest; Iodine; Sedation	Subtotal thyroidect.	Fever, rash	See text
16. M.H. female, 29	Diffuse Ex.	2 years	30	14 days	1 gm. thiouracil	None	None	None	Previously treated with iodine, not for 3 months prior to thiouracil
17. A.S. female, 31	Diffuse Ex.	6 months	70–80	14 days	1 gm. thiouracil	Bed-rest;	Subtotal thyroidect.	None	Biopsy before treatment. Thiouracil used as preop. treatment
18. A.M. female, 65	Nodular	Goiter 30 years; toxic 4 months	60–70	10 weeks	1 gm. thiouracil, then 2 gm.	Iodine; Bed-rest; Sedation	Thyroidectomy	None	See text
19. E.C. male, 49	Diffuse	2 years	30	14 days	0.8 gm. thiouracil	Sedation; Bed-rest	None	Rash, fever, Arthralgia	
20. E.C. female, 45	Diffuse	5 months	25	9 days	1 gm. thiouracil	None	Recurrence op. 18 years ago	Rash, fever, arthralgia, jaundice	
21. C.M. male, 61	Diffuse Ex.	6 months	50	11 days	1 gm. thiouracil	None	None	None	

ceptions were those patients who did not respond to the standard initial daily dose of 1 gm. of thioracil but showed improvement after receiving a larger dose for one to two weeks and one patient with iodine-fast toxic nodular goiter who responded only after four weeks of treatment.

DOSAGE

The dosage of thiouracil only will be discussed since our experience with thiourea is limited. As soon as thiouracil became available we discontinued the use of thiourea because of the high incidence of toxic manifestations.

Treatment was started routinely with 1 gm. of thiouracil daily in 5 doses of 0.2 gm. each, distributed evenly throughout the day. No attempt was made to determine the minimal effective dose. After the full effect was achieved as gauged by clinical improvement and return of pulse-rate and BMR to normal, two courses were open for "permanent maintenance" of those patients scheduled for medical treatment. Inasmuch as experimental and clinical observations have shown that the effect of the drug is reversible, treatment may be either a) discontinued until symptoms and signs of thyrotoxicosis recur and then reinstituted (intermittent treatment), or b) maintained and an attempt made to establish a small "permanent maintenance dose." The latter course was pursued in 13 cases, the quantity of thiouracil being gradually reduced to a maintenance dose of 0.1 to 0.4 gm. daily. Evidences of myxedema developed in two cases during this period of adjustment, the BMR dropping to −16 and −17 respectively, while on daily dosage of 0.6 gm. and 0.8 gm., the serum cholesterol rising to 452 mg. per cent in one case. Both patients were drowsy and tired and the eyelids were puffed. These symptoms disappeared and the BMR returned to normal within one week after cessation of treatment, which was then resumed at a lower dosage level. One of the two patients complained of dryness of the hair and brittleness of the nails for several weeks; these symptoms disappeared only after further dosage reduction.

In three cases no improvement was achieved with an initial dosage of 1.0 gm. (five times 0.2 gm.) and a typical satisfactory response was obtained when this was increased to 2 gm. daily (five times 0.4 gm.). No ill effects were observed at this dosage level, which was reduced after the full effect was achieved. One of these three patients has subsequently been maintained adequately with 0.2 gm. daily.

TOXIC MANIFESTATIONS

A. *Thiourea.* Our experience is limited to six patients, four and possibly five of whom had toxic manifestations. One developed a maculopapular eruption and vomited severely even when the drug was given in enteric-coated capsules. Because of the severe vomiting, treatment was discontinued; this patient was operated upon after preparation with iodine and made an uneventful recovery. Maculopapular eruption and fever occurred in three other cases and disappeared two to three days after treatment was discontinued. No significant changes in the blood picture were observed. Two of these patients were subsequently treated with thiouracil.

B. *Thiouracil:* We have observed a maculopapular eruption in three instances (*Cases 1, 19, 22*), the rash disappearing two days after treatment was discontinued. In two patients (*Cases 19, 20*) it was associated with chills, fever and pain in the joints. The toxic reaction occurred nine days after treatment was started, at dosage levels of 0.8 gm. and 1.0 gm. daily respectively. In one patient (*Case 19*) a second similar reaction occurred three days after treatment had been resumed with 0.4 gm. daily, and a third six hours after a single dose of 0.2 gm. In *Case 20* a second and third reaction occurred with successively smaller doses and after shorter intervals, the third reaction occurring two hours after a single dose of 0.2 gm. In this case subclinical jaundice developed (urine urobilinogen, 1:100; serum bilirubin, 2.5 mg. per cent; dye retention, 60 per cent). The serum bilirubin returned to normal within two days. In the third patient (*Case 1*), toxic manifestations, including moderate leucopenia (2,500), first appeared after eight months of treatment, following an upper-respiratory-tract infection. The leucocyte count returned to normal and the rash disappeared three days after the drug was discontinued. Forty-eight hours after treatment was resumed the leucocyte count fell again but the rash did not reappear.

Astwood (7) has reported one case of drug-rash following thiourea and one case of agranulocytosis following thiouracil. Himsworth (9) noted nausea and vomiting in cases treated with thiourea. Gabrilove and Kert (10) reported toxic manifestations in three cases treated with thiouracil, fever, lymphadenopathy and dermatitis occurring in one case, fever and dermatitis in a second, and leucopenia in a third. Sloan and Shorr (11) mention one instance of mild jaundice following the use of thiouracil.

THE GOITER

Thiourea and thiouracil are goitrogenous in normal animals, the gland increasing to two and three times its normal size after several weeks of treatment. An increase in the size of the thyroid gland was not observed in any of our cases and in one case it seemed to become appreciably smaller. However, accurate evaluation of change in size is difficult since the gland usually becomes much softer after administration of thiouracil.

Histological studies were made of six thyroids, four obtained at operation and two at autopsy. In one case a biopsy specimen was obtained before thiouracil treatment was instituted which was compared with the gland obtained at operation following treatment with thiouracil. These findings, which will be published in detail elsewhere, generally bear out what would be expected on the basis of animal experimentation and what has been described by Rawson *et al.* (12) in human thyroids. Hyperplasia characteristic of the thyrotoxic gland is increased, the cells frequently being arranged in nests rather than in follicles. In one instance (*Case 6*), both thiouracil and iodine were given to a patient who had received iodine for three months previously. This gland also showed considerable hyperplasia, whereas Rawson *et al.* (12) found little hyperplasia after thiouracil in glands previously exposed to iodine. It should be noted that in our case the response to iodine had been unsatisfactory.

Extensive lymphoid infiltration was observed in *Case 12*, but since no biopsy was obtained prior to medication it cannot be stated whether this had developed or increased during thiouracil treatment. *Case 17* showed no lymphoid infiltration either in the pre-treatment biopsy specimen or in the operative specimen obtained after thiouracil medication.

PRE-OPERATIVE USE OF THIOURACIL

In two cases (Surgical Service A, Pennsylvania Hospital) thiouracil was given in preparation for surgery. An abundant carbohydrate-high protein diet and sedatives were also given when necessary but no iodine was used.

The operative and post-operative course was satisfactory in both cases. Rawson *et al.* (12) have reported similar experiences.

THIOURACIL IN IODINE-FAST THYROTOXICOSIS

One patient (*Case 18*), a white woman 54 years of age, had had a nodular goiter for thirty years and developed manifestations of thyrotoxicosis six months prior to admission. Inasmuch as the goiter extended substernally and was displacing the trachea, it was felt that surgery was indicated. This patient was given 5 minims of Lugol's solution three times daily. After three weeks there was no improvement in either BMR (+40 to +50) or tachycardia. According to the most careful information obtainable she had not received iodine prior to her hospital admission. Thiouracil treatment was then given (1 gm. daily) and the iodine was continued. During this period she developed a severe tracheobronchitis, with fever. After 10 weeks of treatment the BMR had fallen to +25 and the patient was regarded as a satisfactory risk. However, thyroid crisis developed 24 hours after operation, and death occurred after 72 hours. This patient evidently was operated upon too early. Probably continuation of treatment for a longer period would have made operation safe.

In another case of diffuse toxic goiter (Surgical Service A, Jefferson Hospital, *Case 15*) there was no response to iodine after two weeks (BMR +46, pulse-rate 120). Thiourea was given for ten days (2 gm. per day) simultaneously with iodine but was discontinued because of toxic manifestations (fever, eruption) which disappeared promptly after the drug was discontinued. The BMR had fallen to +25 and the pulse-rate to 90. Operation was performed with an uneventful post-operative course.

Whether pre-operative treatment with thiouracil offers any advantage over iodine in the

average case cannot be stated at the present time. It appears probable, however, that preoperative use of thiouracil may be effective in cases in which the response to iodine is unsatisfactory. Rawson *et al.* (12) have drawn attention to the fact that the effect of thiouracil is delayed after treatment with iodine. This appeared to be true in *Case 19* but not in *Case 15*. It should be noted that the latter patient received thiourea. Future experience will determine whether it is advisable to discontinue iodine medication when its inefficacy has been demonstrated and to administer thiouracil alone, or whether both drugs should be given simultaneously, as was done in our cases.

THIOURACIL VERSUS OPERATION

Whether thiouracil will prove to be a satisfactory substitute for the surgical treatment of diffuse toxic goiter cannot of course be stated on the basis of present limited experience with this form of therapy. The chief advantages of treatment with this agent would seem to lie in the possibility of gradual, controlled suppression of thyroid hyperactivity and the ready reversibility of the effect of the drug. This would seem preferable to sub-total thyroidectomy with its inherent dangers of post-operative myxedema and residual or recurrent thyrotoxicosis, entirely apart from the ordinary surgical risk, small as this may be in the hands of an experienced thyroid surgeon. Disadvantages of the use of thiouracil are the possible necessity for permanent treatment and the possible development of toxic manifestations. Whereas much more experience is necessary before final evaluation of this therapeutic procedure is possible, it promises to be of great value in cases in which operation is inadvisable or contraindicated.

There are three such cases in our series. In *Case 4*, a white woman, aged 34, thyrotoxic manifestations had started insidiously and had become gradually worse over a period of six years. During the past year she had become very much more nervous, with palpitation, weight-loss and profuse sweating. Weakness and lassitude prevented her from performing even simple household duties. She was admitted for operation to Surgical Service A at Jefferson Hospital and received routine preoperative iodine medication with bed-rest, high-calorie diet and sedatives. The BMR fell from +25 to +7, but nervousness and tremor persisted; there was no increase in weight; the pulse rate remained above 100. Operation was attempted on four occasions but the pulse rate rose to 140–160 each time under anesthesia and it was decided to resort to medical management. Thiouracil was given with iodine until the pulse rate fell to 80–90, when the iodine was withdrawn. Thiouracil was continued, the dose being gradually reduced to 0.1 gm. daily. While on a higher dosage this patient developed signs of myxedema which disappeared promptly after withdrawal of the drug for one week. She has now been well for eight months, is doing her housework, caring for two children, and leading a normal life. She is still taking 0.1 gm. daily.

Case 5: A white woman, 50 years of age,[4] had been receiving psychiatric treatment for psychoneurosis for many years. Following a major emotional upset (death of her mother) she developed thyrotoxicosis with a diffuse goiter which improved after treatment with iodine, the BMR falling from +43 to +13. The psychiatrist and the consulting surgeon felt that this patient presented a grave operative risk, namely, the likelihood of developing a post-operative psychosis. Iodine was discontinued and thyrotoxic manifestations reappeared with weakness, weight-loss, sweating, tremor, vasomotor instability and a BMR of +36. She was given thiouracil, 1 gm. daily, the dose being reduced after a full effect was achieved, and is now maintained in an apparently normal state with 0.2 gm. daily.

Case 11: A colored man, aged 32, was admitted to Surgical Service A at Jefferson Hospital because of recurrent thyrotoxicosis one year after sub-total thyroidectomy for diffuse toxic goiter. He was again operated upon, with little or no improvement. Tachycardia persisted and the BMR was +30 three weeks after operation. Treatment with thiourea was begun and within three weeks the BMR had fallen to normal values (+10); the patient felt well and resumed work. He then had an "upset stomach" for which he did not report to the

[4] Courtesy of Dr. R. A. Matthews.

clinic but stopped medication of his own accord. When he returned to the clinic his condition was satisfactory. He has been under observation for seven months, during which period he has received no medication, feels perfectly well, and is performing hard work.

SUMMARY AND CONCLUSIONS

The effect of thiourea and of thiouracil was studied in 21 cases of thyrotoxicosis.

It was found that thyrotoxicosis can be suppressed with either drug.

Thiourea proved to be more toxic and was discontinued as soon as thiouracil became available.

Toxic manifestations from thiouracil, consisting of cutaneous eruption, fever, arthralgia, leukopenia and jaundice, were observed in three cases.

Improvement was usually noticeable after 4 to 6 days of treatment, with complete suppression of thyrotoxic manifestations after 2 to 3 weeks.

One gram of thiouracil was effective in most cases but in three instances no response was achieved with 1 gm. and a full effect was obtained with 2 gm.

Thiouracil was used for pre-operative treatment in three cases, the pre-operative and post-operative course being satisfactory in two and death in thyroid crisis occurring in the third, who had also received iodine pre-operatively.

The drug proved particularly valuable in cases in which operation was deemed inadvisable.

An attempt was made to establish a permanent maintenance-dosage level rather than to employ intermittent treatment. After full effect was achieved, doses as small as 0.1 to 0.2 gm. daily proved satisfactory.

Evidences of myxedema developed in two cases and subsided after the drug was temporarily discontinued.

REFERENCES

1. MacKenzie, C. G., and J. B. MacKenzie: Effect of sulfonamides and thiourea on the thyroid gland and basal metabolism. *Endocrinol.* 32: 185. 1943.
2. Astwood, E. B., J. Sullivan, A. Bissell and R. Tyslowitz: Action of certain sulfonamides and of thiourea upon the function of the thyroid gland of the rat. *Endocrinol.* 32: 210. 1943.
3. Dempsey, E. W., and E. B. Astwood: Determination of the rate of thyroid hormone secretion at various environmental temperatures. *Endocrinol.* 32: 509. 1943.
4. Baumann, E. J., N. Metzger and D. Marine: Mode of action of thiourea on the thyroid gland of rabbits. *Endocrinol.* 34: 44. 1944.
5. Keston, A. S., E. D. Goldsmith, A. S. Gordon and H. A. Charipper: The effect of thiourea upon the metabolism of iodine by rat thyroid. *J. Biol. Chem.* 152: 241. 1944.
6. Astwood, E. B.: The chemical nature of compounds which inhibit the function of the thyroid gland. *J. Pharm. Exp. Therap.* 78: 79. 1943.
7. Astwood, E. B.: Treatment of hyperthyroidism with thiourea and thiouracil. *J. Am. Med. Assn.* 122: 78. 1943.
8. Williams, R. H., and G. W. Bissell: Thiouracil in the treatment of thyrotoxicosis. *New England J. Med.* 229: 97. 1943.
9. Himsworth, H. P.: Thyrotoxicosis treated with thiourea. *Lancet* 2: 465. 1943.
10. Gabrilove, J. L., and M. J. Kert: Sensitivity to thiouracil. *J. Am. Med. Assn.* 124: 509. 1944.
11. Sloan, H. S., and E. Shorr: Metabolic effects of thiouracil in Graves' disease. *Science* 99: 305. 1944.
12. Rawson, R. W., A. D. Evans, J. H. Means, W. C. Peacock and J. Lerman: The action of thiouracill upon the thyroid gland in Graves' disease. *J. Clin. Endocrinol.* 4: 1. 1944.

Precocious Sexual and Somatic Development in a Male Infant with a Presacral Teratoma Containing Androgen-Producing Tissue

With a Discussion of the Mechanism of Precocity Caused by Teratomas[1]

ALFRED E. RHODEN, M.D.

From the Department of Pathology, University of Arkansas, School of Medicine, Little Rock, Arkansas

CASES OF teratoma associated with precocious sexual and somatic development are of utmost rarity. In this paper, the literature on teratoma with precocity is reviewed, a unique case of presacral teratoma with androgenic tissue causing precocity is presented and the mechanism by which teratomas cause precocity is discussed.

LITERATURE ON TERATOMA WITH PRECOCITY

An accurate appraisal of the literature was difficult since some reports of tumors associated with precocity are dated long before the recognition of certain lesions capable of causing precocity such as the interstitial-cell tumor of the testis and the granulosa-cell tumor of the ovary. The proper classification of some tumors seemed impossible to achieve since histological findings were either not given or appeared inadequate.

Teratoma with precocity in the male. The only undisputed cases of teratoma associated with precocity seem to be those arising from the pineal gland. The tendency has been to consider factors other than the teratoma itself as responsible for the precocity. Marburg (1) thought that the destruction of the pineal eliminated an inhibitory influence on sexual maturation. The opinion most generally shared today is that the concomitant hypothalamic involvement gives rise to the precocity (2). Askanazy (3) however, claimed that a teratoma itself, arising from the pineal or elsewhere, may cause precocity.

Askanazy referred to Sacchi's testicular tumor as well as to tumors arising from the kidney, adrenal and pineal, He considered these tumors which were accompanied by varying degrees of precocity to be teratomas. He conceded, however, that in the case of the renal and adrenal tumors there was no histological evidence to support his opinion.

Sacchi (4) in 1895 described somatic and sexual precocity in a 5½ year old boy associated with a growth arising in the left testis. The removal of the tumor at the age of 9½ years was followed by marked regression of the precocity. A review of Sacchi's paper revealed nothing in the histological description of the growth to suggest a teratoma. Its appearance was apparently that of an alveolar carcinoma. It is possible, however, that at the time of examination the immature, carcinomatous tissue had largely blotted out the teratoma from which it arose. Furthermore, Ewing's (5) view that the great majority of testicular tumors arise on a teratomatous basis is generally accepted. It is therefore suggested that Sacchi's case was indeed, the first report of precocity in the male associated with a teratoma which did not arise in the pineal region though definite proof of this is lacking. In this connection it is interesting to note that Sacchi's case was also interpreted to be an interstitial-cell tumor of the testis (6).

The case to be presented appears therefore

[1] Research paper No. 547, Journal Series, University of Arkansas.

to be the first authentic instance of a teratoma arising in a male from a site other than the pineal region and accompanied by precocious somatic and sexual development.

Teratoma with precocity in the female. A case of ovarian teratoma associated with precocious sexual and somatic development in a girl was reported by Harris (7). The patient, when seen at the age of five years and ten months, showed developed breasts, axillary and pubic hair. Her weight and height were those of an average girl of nine years. She gave a history of six regular menstrual periods. A large ovarian teratoma was removed. It showed derivatives of all germ layers. Large areas of the teratoma resembled an adenocarcinoma. The removal of the tumor was followed by regression of the precocious development with cessation of menstruation until the age of twelve years and nine months. No hormone studies were performed nor was an explanation of the association of teratoma and precocity ventured except that Askanazy's concept was mentioned. This concept will be discussed subsequently.

Harris mentioned Fusino's case, which was reported in 1893. Menstruation occurred in a five-year-old girl with an ovarian teratoma and recovery from the precocity followed operation.

FIG. 1. The external genitalia of a nine-month-old infant. Note large penis and scant pubic hairs. Some edema of the prepuce developed following catheterization.

Harris also cited the four cases of ovarian sarcoma which Askanazy had collected, believing them to be truly embryonal teratomas. The patients showed the following symptoms individually or in combination: genital hemorrhages, growth of pubic hair, mammary hypertrophy and abnormal height. It is probable that these cases of so-called ovarian sarcoma were granulosa-cell tumors.

Teratoma of the pineal with precocity, though found repeatedly in the male, has apparently not been observed in the female (Bochner and Scarff, 1938; Weinberger and Grant, 1941).

CASE REPORT

A nine-month-old, white, male infant was admitted on August 23, 1943, at the Arkansas Children's Hospital. The mother stated that the child had not voided during the preceding two days and had vomited repeatedly. She also noted that the child was abnormally developed for its age.

Present illness. The parents first noticed that the baby, two months prior to admission, did not void in a stream, but dribbled. The disturbance of urination had become progressively worse. About two weeks prior to admission, constipation occurred.

Past history. The child was born at term in normal delivery. The birth weight was 9½ lbs. The mother noticed that the child grew much more rapidly than her other children. The infant had a remarkable appetite. It had diarrhea during the summer. No other illnesses were recalled.

Family history. There were four other children. No other instances of abnormal development were known.

Physical findings. The fairly well-nourished infant appeared acutely ill, was restless and had a temperature of 100° F. rectally. Its precocious development was apparent from the following findings. The anterior fontanelle was almost closed (normal closure—17–18 months). Eight teeth were present, four upper and four lower incisors (dental age—approximately one year). The height was 30½ inches (the average normal height at the age of 1½ years), the arm span was 28½ inches, symphysis to vertex 18 inches, symphysis to sole 12½ inches. The

weight was 22 lbs. 13 oz., one pound in excess of the average weight of a one-year-old child. The penis was markedly enlarged, measuring 6 cm. in length and 4 cm. in circumference. The scrotum was enlarged, its skin was thick and wrinkled. Scanty, coarse, long pubic hairs were present (fig. 1).

The eyes moved freely in all directions. The ocular fundi appeared intact. The reflex status was normal. An acneiform eruption was seen on the face and upper back. Both testes were in the scrotum and appeared to be normal in size. The heart rate was 150 per minute. The systolic blood pressure was 130 mm. Hg. systolic, the diastolic pressure was not recorded.

The abdomen was protuberant and tender. The distended urinary bladder extended to the umbilicus. A round mass about 4 cm. in diameter was palpated over the lower back, to the left of the midline and adjacent to the tip of the sacrum. It was non-tender and fixed to deep structures. The skin was freely movable over it. Rectal examination revealed a large mass which filled the pelvis posteriorly and to the left. It did not fluctuate and did not vary in size when the child strained or cried. The rectal mucosa was freely movable over the mass. It seemed to be connected with the mass felt adjacent to the sacrum posteriorly. Catheterization did not reduce its size.

Laboratory findings. The blood findings were: RBC 3,900,000; Hb. 70%; color index 0.9; WBC 32,050; differential count—segmented polymorphonuclear leucocytes 74%, stabs 2%, lymphocytes 24%.

The urine was cloudy and acid; the specific gravity was 1.020; albumin, one plus; sugar, negative. Microscopically there were seen 200–300 WBC and 10–15 RBC per high-power field. X-ray plates of the skull and pelvis revealed no abnormalities. A plate of the arm showed the capitellar epiphysis of the humerus to be developed (normally at 17 months).

A Friedman test, employing 20 cc. of urine, and a Kline test were negative.

Course: During its stay of nine days at the hospital, the infant dribbled urine constantly. It was catheterized at regular intervals. The N.P.N. was 73 mg. per cent on admission, but dropped to 54 mg. per cent after two days. The infant continued to have urinary retention and its temperature rose to 103° F. A deep-seated obstruction of the urethra was encountered with the catheter. The day prior to the exitus, the N.P.N. was 83 mg. per cent. Death followed a generalized convulsion.

For reasons to be stated in the discussion, the precocity in this case was considered to be of adrenal cortical origin. Adreno-cortical tumors giving rise to precocity are often malignant growths. It was therefore thought that the pelvic mass might have originated from a primary adrenal tumor. Since tumors may occur from aberrant adrenal cortical tissue (Kolodny, 8), it was considered a remote possibility that the pelvic tumor was a primary lesion. The critical condition of the child prevented any attempts to demonstrate an adrenal tumor by means of pyelography and retroperitoneal air insufflation. Hormone excretion studies other than the Friedman test were unobtainable.

FIG. 2. The presacral teratoma, arising within the pelvis between the sacrum and the rectum, photographed from above after removal of the viscera. The tumor was easily shelled out.

The clinical diagnosis was: 1) sexual and somatic precocity, probably of adrenal origin; 2) pelvic tumor, probably of adreno-cortical tissue, causing urinary obstruction and pyelonephritis.

AUTOPSY FINDINGS

The autopsy was performed two hours after death.

Head. The brain was normal. The pineal region and the floor of the third ventricle were given close attention. The pituitary was normal in size. Sections revealed nothing unusual.

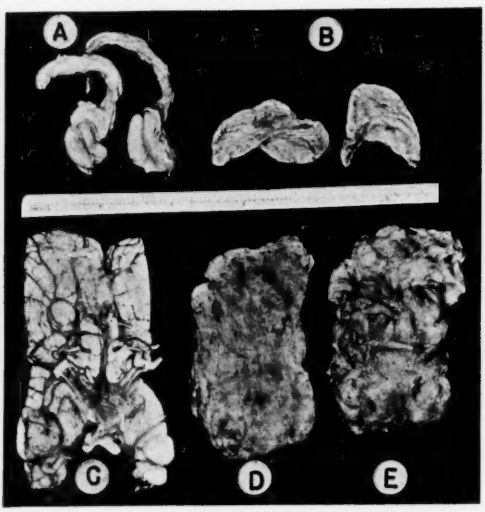


FIG. 3. A: the normal-sized testes
B: the normal-sized adrenal glands
C: the base of the brain showing the normal hypothalamus
D: the cut-surface of the teratoma with multiple minute cysts
E: the external surface of the teratoma which was nodular and largely encapsulated.
The interpolated scale is 6 inches long.

Chest. The thymus was small, confined to the upper third of the anterior mediastinum and weighed six gm.[2] (Normal weight at birth is about 15 gm. and increases until puberty.) Microscopic sections revealed calcification of great numbers of Hassal bodies (fig. 7).

Abdomen. The adrenals were normal in size. The right adrenal gland weighed 2.1 gm., and the left, 2 gm. The disappearance of the "androgenic" or x-zone was practically complete. No aberrant adrenal cortical tissue was found. A large tumor filled the pelvis, pushed the bladder upward and forward, and caused stretching and obstruction of the urethra. The bladder wall was thickened, its lumen was dilated and its mucosa was the site of a necrotizing, hemorrhagic inflammation. Both ureters were dilated and inflamed. The kidneys revealed dilated and inflamed pelves. Hemorrhagic streaks radiated towards the cortex. The lumen of the rectum was narrowed as a result of pressure by the tumor. The prostate appeared larger than normal for an infant of this age. Microscopically, numerous dilated glands were seen, lined by a tall epithelium and in places filled with secretion (fig. 6). The testes were small and weighed 1.9 gm. respectively, with the epididymis attached. The seminiferous tubules of the testes were undeveloped; their lumina were closed. The interstitial cells were not conspicuous.

Pelvic tumor. The tumor was irregularly spherical, measured 14×12×9 cm., with a nodular surface, and was largely encapsulated. It was wedged in the pelvis, situated to the left and posterior to the rectum, its upper pole rising 2 cm. above the pelvic inlet (fig. 2). Its upper surface was covered by peritoneum. The growth was easily shelled out except at its inferior and posterior surface where it was attached to the pelvic floor and extended beyond the pelvic confines to give rise to the mass palpated externally adjacent to the sacrum. On section it was found to be riddled with small, mostly smooth-walled cysts. Their contents consisted of a clear fluid which was occasionally darkly discolored. Some cysts contained gelatinous material. The tissue between the cysts varied in consistency and color. Some areas were dense and white while others were friable and hemorrhagic.

The microscopic appearance was characteristic of a teratoma, presenting derivatives of all three germinal layers in varying stages of maturity. An occasional tendency at grouping together of tissues normally associated in the formation of organs was noted, but for the most part the various tissues were haphazardly mingled. Cysts were lined by single rows of cubical and columnar or by stratified epithe-

[2] All weights were obtained after fixation.

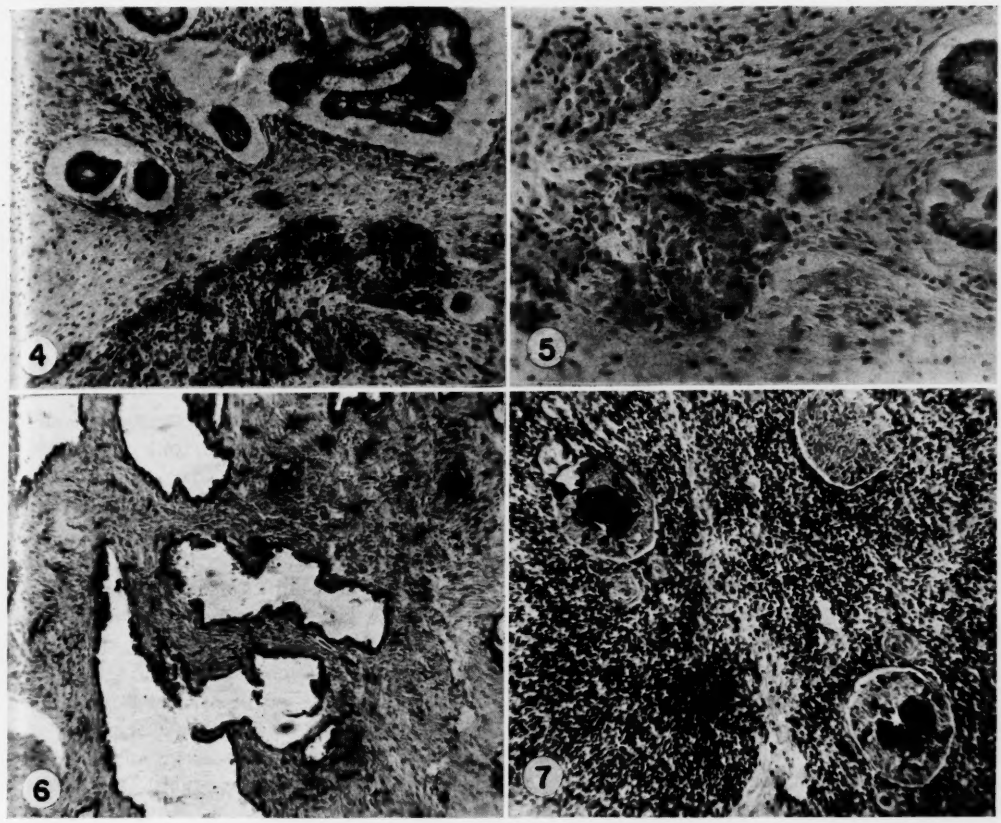


FIG. 4. A large island of "androgenic" cells from the teratoma. In addition, one sees glands lined with columnar epithelium containing numerous goblet cells.
FIG. 5. "Androgenic" cells under higher magnification. Their outlines are angular and they are arranged in small nests and strands surrounded by a capillary network.
FIG. 6. The prostate, showing marked development of the glands.
FIG. 7. The atrophied thymus shows calcified Hassal's corpuscles.

lium. Ciliated cells, goblet cells and areas of keratinization were seen. Bundles of smooth muscle surrounded some of the epithelium-lined spaces. Small spaces were lined by what seemed to be primitive neuro-epithelium. Immature epithelial cells in gland-like arrangement or forming plexiform strands occupied large areas. The stroma was fibrotic in some areas, mucoid or myxomatous in others. Though some immature, epithelial cells appeared atypical and seemed to invade the stroma irregularly, there was no evidence of invasion of vessels, of extension into adjacent organs, or of metastasis.

The question now arose whether the teratoma contained some demonstrable endocrine structures which could be made to account for the precocity. A survey was made of endocrine structures known to be capable of producing precocity in the male as well as of structures thought on theoretical grounds to be capable of doing so. These structures, which will be dealt with subsequently in the discussion, were "androgenic" adrenal cortex, Leydig's interstitial cells, anterior-pituitary tissue and chorionic epithelium. They were searched for in sections taken systematically throughout the tumor.

Androgenic tissue in teratoma. Acidophilic, epithelioid cells were found with great consistency in almost every slide. Their outlines were angular. Their cytoplasm was finely granular

and contained in areas varying-sized vacuoles. Their arrangement, in small nests and strands, surrounded by a dense capillary network, was highly suggestive of an endocrine structure (fig. 4, 5). Though their number in individual sections was rather small, their total amount was apparently considerable. A detailed discussion of these cells follows.

Pathologico-anatomical diagnosis. 1) Presacral teratoma with pressure on neck of bladder and rectum with resulting a) necrotizing cystitis; b) bilateral hydro-ureter; c) bilateral pyelonephritis.

2) Androgenic tissue in the teratoma.

3) Somatic precocity (increased weight and height; advanced dental and bone age) together with precocity of secondary sexual characteristics (enlarged penis and scrotum, functional activity of prostate).

4) Involution of the thymus.

Bio-assay of the teratoma for androgens. The tumor, weighing 55 gm., and the solution in which it was suspended were extracted by the method of Gallagher and Koch (9). A similar amount of kidney tissue from the same case was subjected to an identical extraction. Four male albino litter-mate rats were castrated at the age of 30 days. The following day, one animal received the first of five daily injections with the tumor extract. Another animal was injected similarly with the kidney extract. All animals were killed at the age of 36 days. The weight of their seminal vesicles and prostate was as follows:

	sem. ves.	prostate
Rat 1: tumor extract	5.9[1]	46
Rat 2: kidney extract	5.0	18
Rat 3: control	5.1	27.6
Rat 4: control	4.8	24

[1] All weights in mg.

Since the amount of hormone recoverable from 55 gm. of preserved tumor tissue was thought to be small, the entire yield was injected into a single rat. The experiment had therefore from necessity to be conducted on a small scale. The kidney extract was used to eliminate any possibility that the effect was the result of a high androgen content present in the various tissues. It also indicated whether or not the effect was due to non-specific tissue extracts.

DISCUSSION

Clinical analysis. The following lesions have been shown to be capable of producing precocious puberty in boys.

a) a pineal-hypothalamic or hypothalamic lesion (pineal tumor with hypothalamic involvement; hypothalamic tumor, malformation, inflammation or internal hydrocephalus); b) an adrenal cortical tumor; c) an interstitial-cell tumor of the testis.

The lack of any evidence—neurologic, roentgenologic or from the past history (for instance measles encephalitis)—pointing to cerebral involvement tended to rule out pineal-hypothalamic changes.

In the few reported instances of interstitial-cell tumor of the testis with precocity, the palpable enlargment of one testis gave the clue to the diagnosis in every instance (10). No testicular enlargement was present in this case.

In cases of precocious puberty resulting from hypothalamic involvement, enlarged testes, often with evidence of spermatogenesis, are found with great frequency (2). On the other hand, with adreno-cortical lesions the testes are apt to be small and without spermatogenesis (Grollman, 11).

On the basis of this clinical evidence, the precocity was attributed to an adrenal cortical tumor.

Endocrine lesions capable of causing precocity in the male. a) The pineal-hypothalamic group of lesions is thought to effect precocity by means of an increased output of gonadotropic hormone, from the anterior pituitary.

b) Adrenal cortical tissue has caused precocity in males in numerous instances (12). It is the source of an androgenic hormone (androsterone), which is structurally as well as functionally closely related to the androgenic hormone elaborated by the testis (testosterone).

c) Leydig's interstitial cells, thought to be the actual producers of the testicular androgenic hormone, caused precocity in only three reported instances. The authenticity of the fourth case, reported by Sacchi, seems open to challenge.

d) Lesions of the pituitary gland proper have apparently not been shown to cause precocity

in the male. However, an over-development of the sexual characteristics has been observed in the early stages of acromegaly which was associated with increased amounts of gonadotropic hormone (13). The possibility of functioning, ectopic pituitary tissue in a teratoma needs to be considered. The remarkable case of Cushing's disease thought to be caused by ectopic pituitary tissue in an ovarian teratoma attests to such a possibility (14).

e) Finally, there is the chorionic gonadotropin to be considered. Elaborated by trophoblastic tissue, it has been demonstrated with teratoma of the testis, assuming excessive proportions when the lesions were largely or wholly composed of chorionic epithelium. There is evidence that the injection of chorionic gonadotropin in considerable amounts may lead to precocious puberty (15). Yet no reference was found to precocity caused by a tumor elaborating chorionic gonadotropin.

Androgenic tissue in teratoma. Since the interpretation of the structures considered to be capable of producing androgenic hormone is of greatest importance in the analysis of this case, either slides or tissue from the teratoma were submitted to others for their opinions.

Dr. W. O. Nelson, Wayne University, carried out a study with the following preparations:

1. Hematoxylin and eosin
2. Mallory's triple stain
3. Masson's stain
4. Iron hematoxylin and erythrosin
5. Broster-Vines stain
6. Sudan III
7. Post-osmication
8. Schultz reaction
9. Mounts for study with petrographic microscope.

Preparations 1–4 confirmed the findings noted previously. The Broster-Vines preparation gave no useful information. The Sudan III and post-osmication preparations both revealed lipoid droplets, varying from small pinpoint droplets to droplets which virtually filled the cells. They corresponded with the vacuoles seen in hematoxylin-eosin preparations. The droplets gave a positive Schultz reaction which is said to be specific for cholesterol and its esters. The examination of the unstained tissue under the petrographic microscope revealed little birefringent material.

Dr. Nelson commented on the basis of these findings that the cells in question may be adrenal cortical, Leydig's interstitial cells or hepatic cells. He felt inclined to dismiss the possibility of their being Leydig cells since they presented too heavy granulation and nuclei which were not characterstic. In addition, none of the cells showed crystalloids or pigment granules. The absence of these, however, might be due to the extreme youth of the patient. He thought the cells capable of elaborating a steroid hormone. They were the only cells in the teratoma which may be considered the source of such hormone.

Dr. A. Grollman, Bowman Gray School of Medicine, agreed that there were numerous areas in the tumor which in all respects resembled "androgenic" tissue from the adrenal cortex. He compared the cells with those from an adrenal tumor of a 37-year-old woman with a classical history of an androgenic tumor and found them to display an identical appearance.

Dr. M. A. Goldzieher, New York, felt that the cells in question could be adrenal cortical cells, Leydig's cells or hepatic cells.

The evidence supporting the presence of androgen-producing tissue in the teratoma may be summarized. In the cases of precocity in males free from pineal-hypothalamic involvement, androgen-producing lesions were found to be responsible. The marked development of the secondary sexual characteristics, contrasting with the undeveloped testes, is said to be characteristically encountered with precocity of adrenal cortical origin ("false" sexual precocity, Grollman, 11). Histologically, the teratoma contained cells which resembled closely "androgenic" adrenal cortical tissue and were thought capable of elaborating steroid hormones. A bio-assay of the teratoma suggested the presence of androgenic hormone in the tumor. A fractionation into adrenal cortical or testicular androgens was not attempted. The small size of the thymus supported further the presence of abnormal amounts of androgens which are known to inhibit thymic growth and to lead to involution of the organ (16).

The inclusion of endocrine structures in the teratoma seems interesting. Instances of in-

clusion of adrenal cortical tissue, Langerhans' islands and, especially, of thyroid tissue in teratomas are on record. If the teratoma in this case originated from a primitive germ cell, it would possess the potential faculty to reproduce every tissue in the body. However, if the teratoma arose from a more differentiated cell then its position within the region giving rise to the urogenital ridge may be significant in an attempt to account for either adrenal cortical tissue or testicular interstitial cells.

Causal relationship between teratoma and precocity and mechanism of the precocity. Since the autopsy failed to reveal any other lesion known to give rise to precocity, the question of a causal relationship between the teratoma and the precocity presented itself.

The assumption that precocity may be the result of a teratoma derives support from other endocrine disturbances shown to result from teratomas. Though the great majority of teratomas do not exert hormonal influences, they have been found capable of endocrine functions of a divergent nature. Hyperthyroidism, hypertrophy of the breasts with secretion of colostrum in men accompanied by a positive Aschheim-Zondek pregnancy test and finally, precocious sexual and somatic development in the female may serve as examples of endocrine manifestations associated with teratomas.[3]

Askanazy (3) laid the foundation for our understanding of teratoma with precocity. The mammary hypertrophy and secretion which Starling (1910) induced in virgin rabbits through the injection of the press-juice of rabbit embryos suggested to Askanazy that embryonal tissues contained substances capable of stimulating sex organs. He assumed that a certain amount of embryonal tissue was necessary to induce precocity and that perhaps a certain kind of tissue was needed. His concept has not been amended to conform with our present knowledge.

That a teratoma may be the cause of precocity is illustrated by Harris' case in which the precocity developed together with the ovarian teratoma and regressed upon its removal. It is a highly probable and perhaps the only feasible assumption that the stimulus from a teratoma inducing precocity is hormonal in nature. Embryonal tissues do not generally elaborate a hormone capable of inciting precocity. Teratomas commonly contain considerable amounts of embryonal tissues; however, precocity is observed only on the rarest occasions.

It is suggested that the mammary changes induced by Starling were the result of hormones elaborated by chorionic epithelium. Mammary hypertrophy with secretion of colostrum has been repeatedly observed with tumors containing chorio-epithelial structures. It has characteristically occurred in teratomas of the testis with chorio-epithelial elements. Though chorionic gonadotropin may stimulate precocious development of the genitals, it has already been stated that there are apparently no instances recorded in which a chorion-epitheliomatous tumor has accomplished this. There is no reason to believe that hormones elaborated by chorionic epithelium would be the effective element in all teratomas causing precocious development, though this mechanism may well need to be considered together with other more probable ones.

Various endocrine structures may give rise to precocity. Adrenal cortical tumors and tumors composed of Leydig's cells may cause precocity in males while granulosa-cell tumors may give rise to precocity in females. Teratomas inciting precocity may conceivably contain any of the above-mentioned endocrine structures and additional ones, such as pituitary tissue, which are on theoretical grounds thought capable of causing precocity.

If precocity associated with teratoma may be produced by various endocrine structures within the tumor, a demonstration of those structures by histological means and of the hormone by biological and chemical methods will establish the nature of an individual case.

SUMMARY

A case of precocious sexual and somatic development in a nine-month-old male infant, associated with a presacral teratoma, is presented. The present case appears to be the first authentic report of precocity in the male

[3] A detailed study of "Teratoma and endocrine manifestations" will appear in the near future.

caused by a teratoma arising in a location other than the pineal region.

There is clinical, histological and biological evidence that the teratoma contained androgen-producing cells which were probably of adrenal cortical derivation.

The mechanism of precocity resulting from teratoma is analyzed. It is suggested that various endocrine structures contained in a teratoma may give rise to precocity. In order to establish the exact nature of the precocity in a given case, it is suggested that the endocrine structures and the hormone be demonstrated.

The author would like to express his appreciation for the contributions of Drs. Goldzieher, Grollman and Nelson.

REFERENCES

1. MARBURG, O.: Die Adipositas cerebralis; ein Beitrag zur Kenntnis der Pathologie der Zirbeldruese. *Deutsche Ztschr. f. Nervenh.* 36: 114. 1908–1909.
2. WEINBERGER, L. M., AND F. C. GRANT: Precocious puberty and tumors of the hypothalamus. *Arch. Int. Med.* 67: 762. 1941.
3. ASKANAZY, M.: Chemische Ursachen und morphologische Wirkungen bei Geschwulstkranken, insbesondere ueber sexuelle Fruehreife. *Ztschr. f. Krebsforsch.* 9: 393. 1910.
4. SACCHI, E.: Di un caso di gigantismo infantile (pedomacrosomia) con tumore del testiculo. *Riv. sper. di freniat.* 21: 149. 1895.
5. EWING, J.: Teratoma testis and its derivatives. *Surg. Gynec. & Obst.* 12: 230. 1911.
6. STEWART, C. A., E. T. BELL AND A. B. ROEHLKE: An interstitial-cell tumor of the testis with hypergenitalism in a child of five years. *Am. J. Cancer.* 26: 144. 1936.
7. HARRIS, R. H.: Carcinomatous ovarian teratoma with premature puberty and precocious somatic development. *Surg. Gynec. & Obst.* 24: 604. 1917 and 41: 191. 1925.
8. KOLODNY, A.: Suprarenal virilism in a woman. *J. Am. Med. Assn.* 102: 295. 1934.
9. GALLAGHER, T. F., AND F. C. KOCH: The testicular hormone. *J. Biol. Chem.* 84: 495. 1929.
10. WERNER, A. A., H. I. SPECTOR, A. E. VITT, W. L. ROSS AND W. A. D. ANDERSON: Pubertas precox in a six-year-old boy produced by a tumor of the testis, probably of interstitial-cell origin. *J. Clin. Endocrinol.* 2: 527. 1942.
11. GROLLMAN, A.: The Adrenals. Williams and Wilkins Co., Baltimore 1936.
12. KEPLER, J. E., AND F. R. KEATING: Diseases of the adrenal glands. *Arch. Int. Med.* 68: 1010. 1941.
13. SEVERINGHAUS, A. E.: Cellular changes in the anterior hypophysis with special reference to its secretory activities. *Physiol. Rev.* 17: 556. 1937.
14. KROENKE, E., AND G. W. PARADE: Morbus Cushing bei Ovarialteratom. *Ztschr. f. klin. Med.* 134: 698. 1938.
15. THOMPSON, W. O., AND N. J. HECKEL: Precocious sexual development from an anterior pituitary-like principle. *J. Am. Med. Assn.* 110: 1813. 1938.
16. PERSIKE, E. C.: Involution of the thymus of the young albino rat under treatment with testosterone propionate. *Am. J. Physiol.* 130: 384. 1940.

The Insulin Requirement of Man after Total Pancreatectomy

MARTIN G. GOLDNER, M.D. AND
DWIGHT E. CLARK, M.D.

From the Department of Medicine and the Department of Surgery, University of Chicago, Chicago, Ill.

THE INSULIN requirement of a man after total pancreatectomy, always a matter of physiological interest, has become a problem of clinical importance with the development of modern pancreatic surgery (1, 2).

So far, only theoretical calculations could be made as to the amount of insulin necessary to maintain, in the absence of the pancreas, normal carbohydrate metabolism in man. They were based mainly on experiences with depancreatized animals and their results vary over a wide range. Root (3) estimated that a man of 70 kg. weight would require 200 to 300 units of insulin daily; others (4) arrived at somewhat lower values (70 to 100 units per day). Holm (5) calculated that a starving man would need not more than 10 units per day and that 50 units per day would be sufficient when this man's basal caloric requirement was covered by carbodydrates exclusively. His conclusions were drawn from animal experiments with constant infusions of insulin and glucose. Estimations of the daily insulin requirement on the basis of a hypothetical insulin-glucose equivalent have also been inconclusive. Ratios up to 1:8 have been reported (4–7) though in the diabetic clinic an equivalent of 1 unit insulin for 2 grams glucose has most commonly been found of practical use. Clinical experience has also shown that 100 units of insulin or more per day are required by many diabetic patients, although in some cases the pancreas itself may still produce some insulin.

The first direct observations on depancreatized men have been reported only recently. Rockey (8) observed a man whose carcinomatous pancreas he had removed. This patient survived the operation 15 days. He received 150 gm. glucose daily and his glycosuria could be controlled with about 25 units of insulin. At autopsy, however, a very small amount of pancreatic tissue was found. Brunschwig (9) described a similar case, in which almost as little pancreatic tissue remained. His patient has survived for two and one-half years without clinical evidence of disturbed carbohydrate, fat or protein metabolism. In Priestley's (10) patient who recovered from total pancreatectomy performed because of an insulin-producing islet-cell adenoma, the diabetes could be controlled with 30 units of insulin daily. The disturbances of the fat and protein digestion due to loss of the external pancreatic secretion were not marked.

We have had the opportunity to follow the post-operative course in two patients who underwent total pancreatectomy because of carcinoma involving the head and body of the pancreas.[1] Here again the insulin requirement was less and the insulin sensitivity greater than anticipated and a short report seems of clinical significance although both patients recovered from the operation only temporarily and died on the tenth and eleventh post-operative day respectively. In both instances it was proved at autopsy that the pancreatectomies had been total.

Pre-operatively, both patients had a normal carbohydrate metabolism and were in fairly good nutritional state except for moderate

[1] Acknowledgement is due to Dr. Alexander Brunschwig who kindly allowed us to study one of his patients. The second case was operated upon by one of us (D.E.C.)

anemia. In the first case the tumor had invaded the pancreas from the primary site in the common bile duct and had caused obstructive jaundice. At laparotomy lymph-gland metastases were found. The pancreatectomy was performed for palliative purposes and to alleviate pain. This patient died on the eleventh post-operative day from gastric hemorrhage. The autopsy showed early peritonitis.

The second case was that of a man, aged 45 years, who complained of gradually increasing jaundice and anorexia for 3 weeks and constant right upper quadrant and back pain for 5 months. On Feb. 13, 1943, he was subjected to operation using continuous spinal anesthesia. A large distended gall-bladder and a greatly dilated common duct were found. The head of the pancreas was slightly enlarged, movable and very hard. The body and tail of the pancreas were small and firm. There were no gross metastases. A diagnosis of neoplasm of the head of the pancreas or intrapancreatic portion of the common duct was made. The entire pancreas and the spleen, pyloric part of the stomach and the duodenum, with the exception of its 4th portion, were removed. The neoplasm had extended into the wall of the portal vein and around the celiac axis preventing its complete eradication. A gastrojejunostomy, cholecyst-jejunostomy and jejuno-jejunostomy were performed. Microscopic examination revealed a papillary carcinoma of the intra-pancreatic portion of the common duct with invasion into the head of the pancreas and chronic pancreatitis. This patient survived the operation 10 days and died from hepatorenal failure and uremia.

During the periods of observation the patients did not receive any nourishment by mouth. They were given several blood transfusions and 100 to 150 grams of glucose daily, in 5 per cent solution, as intravenous drip. Patient 1 received also infusions of casein hydrolysate, amigen. Urinalysis and blood sugar estimations were made at regular intervals, mostly four times daily. A solution of insulin zinc crystals was given either subcutaneously or added to the glucose solution and thus entered the system at a very slow rate.

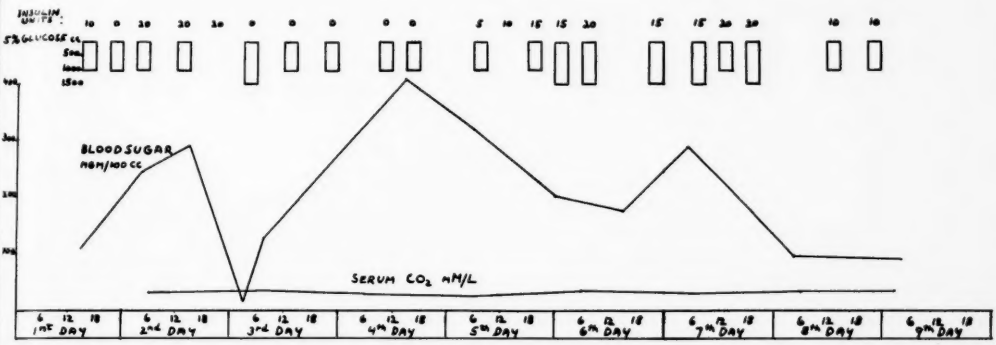


FIG. 1. Blood sugar curve, glucose infusions and insulin dosage during 9 days after total pancreatectomy in Patient 1. The values of the CC_2 combining power of the serum are represented in the lower curve.

The two following graphs illustrate the course of blood sugar, insulin treatment and glucose infusions. The time and amount of the clyses are represented by the columns above the blood sugar curve. The insulin dosage is indicated in the line above the glucose columns. The urinalyses are not represented. Patient 1 excreted about 1–2 grams of glucose daily in a urinary volume of 1500 to 2000 cc. and patient 2 was free of sugar during the first four days and became anuric later.

Patient 1 received within the first 36 hours four infusions of 1000 cc. of 5 per cent glucose solution. Insulin had been added to all except the second one. When it was found that the blood sugar had reached 292 mg. per cent, 20 units of insulin without glucose were given. Six hours later a severe hypoglycemic reaction occurred and the blood sugar had dropped to 14

mg. per cent. Intravenous injection of 50 grams of glucose brought the blood sugar level back to normal (127 mg. per cent). Afterwards the patient appeared to do rather well, showed no ketonuria and only little glycosuria, and no insulin was added to the venoclyses until 48 hours later when the blood sugar had reached 410 mg. per cent. Insulin was then started again, with as little as 5 units. The doses were increased gradually to 10, 15 and 20 units, and no insulin was given without simultaneous glucose infusion. On this management it became possible to keep the blood sugar between 90 and 200 mg. per cent and to avoid further hypoglycemic reactions. The daily insulin requirement was about 50 units on a glucose intake of 150 to 200 gm. The level of the CO_2 combining power of the serum, which was normal throughout the observation period and which is represented at the bottom of the graph, demonstrates that no disturbance of the acid base equilibrium had occurred.

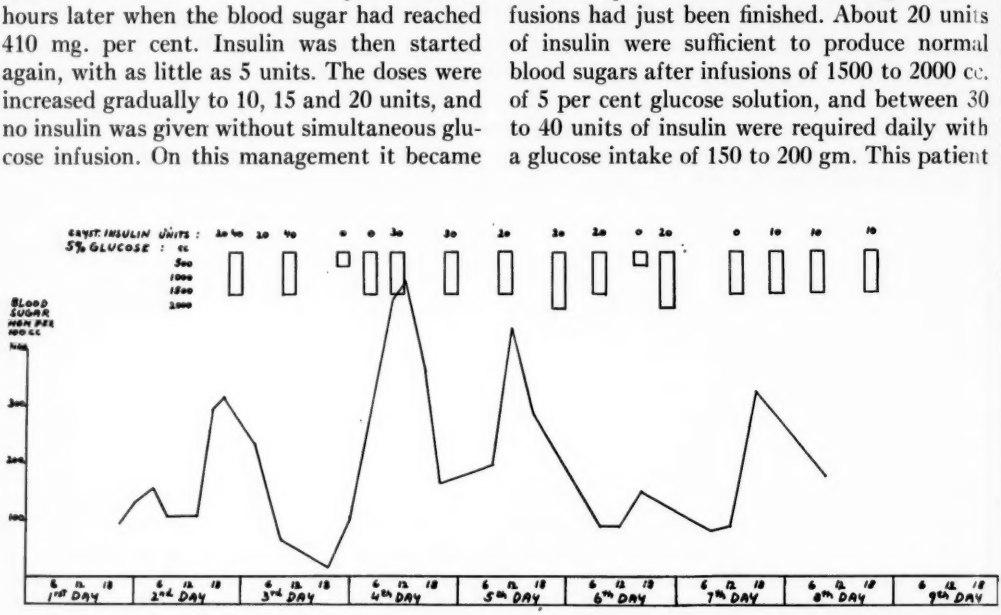


FIG. 2. Blood sugar curve, glucose infusions and insulin dosage during 8 days after total pancreatectomy in Patient 2.

Graph 2 demonstrates that the course of the blood sugar in Patient 2 was essentially the same as with Patient 1. Again there was a slow rise to values around 300 mg. per cent within the first 36 hours, this time without any glucose infusion and not checked by insulin. Then there was a quick response to 20 units of insulin. A severe hypoglycemic reaction followed the simultaneous infusion of 40 units of insulin and of 1500 cc. of 5 per cent glucose solution. The blood sugar dropped to 20 mg. per cent. The second part of the curve shows both the great sensitivity to insulin and the fluctuation of the blood sugar, which probably is partly due to the fact that several of the blood samples were drawn when the glucose infusions had just been finished. About 20 units of insulin were sufficient to produce normal blood sugars after infusions of 1500 to 2000 cc. of 5 per cent glucose solution, and between 30 to 40 units of insulin were required daily with a glucose intake of 150 to 200 gm. This patient died in uremia because of renal failure. His NPN was 125 mg. per cent on the eighth postoperative day. On the same day the total acetone bodies in the blood amounted to 2 mg. per cent only.

A rough calculation of the relationship between insulin and glucose showed that in both patients this ratio was never lower than 1 to 4.

The validity of our observations might be questioned in view of the severe complications in both cases. It should be remembered, however, that complications such as fever, infection, and liver damage usually aggravate a diabetic condition, increase the insulin requirement and reduce the insulin sensitivity. Surgical procedures alone have the same effect in diabetic patients. It is possible, therefore, that the daily insulin requirement would have decreased further if the patients had recovered.

On the other hand, oral feedings at regular intervals and subcutaneous insulin injections instead of the almost constant intravenous infusions might have necessitated somewhat larger amounts of insulin.

From these observations it seems that the depancreatized man requires less insulin and is more sensitive to insulin than many diabetic patients. If the insulin requirement depended on the degree of impaired production of insulin, the opposite should be true. The greatest requirement should exist where no insulin at all can be produced, that is, in the absence of the entire pancreas. Therefore, the question must be raised whether in the causation of diabetes not only lack of insulin but also an insulin-inhibiting mechanism may play a role. Such a factor may operate through an impaired pancreas and may be eliminated if the pancreas is removed entirely. Dragstedt's (11) recent observations that the insulin requirement of partially depancreatized dogs is far greater than that after total pancreatectomy points in the same direction.

SUMMARY

In two patients after total pancreatectomy a very small insulin requirement and a great insulin sensitivity were observed. This phenomenon is of great clinical importance for the post-operative management of patients after pancreatectomy. It may have significance also in any consideration of the etiology of human diabetes mellitus.

REFERENCES

1. Brunschwig, Alexander: The Surgery of Pancreatic Tumors. C. V. Mosby. St. Louis. 1942.
2. Whipple, A. O.: More recent developments in surgical therapy of islet cell tumors. *Proc. Inst. Med. Chicago.* 13: 63. 1940.
3. Root, H. F.: Insulin resistance and bronze diabetes. *New England J. Med.* 201: 201, 1929.
4. (a) Joslin, E. P., H. F. Root, P. White and A. Marble: The Treatment of Diabetes Mellitus, 7th Edition. p. 314. Lea and Febiger. Philadelphia. 1940.
   (b) Houssay, P. A., J. T. Lewis and V. G. Foglia: Effet des injections continues d'insuline chez le chien dépancréaté. *Compt. rend Soc. de Biol.* 101: 214. 1929.
   (c) Baudouin, A., J. Lewin and E. Azérad: Injections continues d'insuline chez les diabétiques. Dose necessaire pour ramener la glycémie à la normale. *Compt. rend. Soc. de Biol.* 127: 378. 1938.
   (d) Greeley, P. O.: The basal insulin requirement of depancreatized dogs. *Am. J. Physiol.* 120: 345. 1937.
   (e) Jensen, Hans F.: Insulin. p. 147. The Commonwealth Fund. New York. 1938.
5. Holm, K.: Ueber die quantitative und optimale Wirkung des Insulins; *Arch. f. exp. Path. u. Pharmakol.* 121: 368. 1927.
6. Miller, M. M., and O. P. Allen: A new mathematical method for the evaluation of endogenous insulin secretion. *Ann. Int. Med.* 13: 636. 1939.
7. Newburgh, L. H., and D. S. Waller: Studies of diabetes mellitus: *J. Clin. Investigation* 11: 995. 1932.
8. Rocky, E. W.: Total pancreatectomy for carcinoma. *Ann. Surg.* 118: 603. 1943.
9. Brunschwig, l.c., page 176.
10. Priestley, J. T., M. W. Comofort and J. Radcliffe: Total pancreatectomy for hyperinsulinism due to an islet cell adenoma. *Ann. Surg.* 119: 211. 1944.
11. Dragstedt, L. R., J. G. Allen and E. M. Smith: Extensive insulin tolerance in diabetic dogs. *Proc. Soc. Exper. Biol. & Med.* 54: 292. 1943.

Effects of Testosterone and of Testosterone Propionate on Protein Formation in Man[1]

JULES C. ABELS, M.D., NELSON F. YOUNG, M.A., AND HOWARD C. TAYLOR, JR., M.D.

From the Memorial Hospital, New York City, New York

THERE NOW IS considerable evidence to show that the parenteral administration of testosterone or its propionate can induce a significant degree of nitrogen retention in normal individuals and in patients with various disorders (1). It has been assumed that the retained nitrogen is used for tissue-protein fabrication, but whether or not serum-protein formation is increased simultaneously has remained unknown. Should the administration of testosterone or testosterone propionate significantly increase the concentration of or amount of total circulating serum protein, then these steroids might prove of considerable clinical value in the prevention of the many complications consequent to hypoproteinemia. This would be especially desirable in patients subjected to intra-abdominal surgery who almost uniformly develop serious degrees of nitrogen loss and hypoproteinemia (2).

CLINICAL MATERIAL AND METHODS

The present study deals with five male subjects. Two of these were normal and three had carcinoma of the stomach. All were fed constant diets which contained 5.0 gm. of carbohydrate, 1.3 gm. of protein, and 1.5 gm. of fat per kg. body weight.[2] The diet was given to the two normal individuals in three equal meals. For the three patients with gastric cancer, the diet was made up of lactose, milk, eggs, salts, dried skimmed milk, and vitamin supplements. This was fed through a gastrostomy opening in six equal parts at four-hour intervals.

The methods for the complete collection of stool and urine have been described in a previous communication (3). No collections were obtained from any individual until he had taken the complete diet satisfactorily for at least 9 days.

The nitrogen content of the stool, urine and food was determined by a micro-Kjeldahl technique (4) and the fat content of the diet by the method of Van Slyke and others (5). The concentrations of serum albumin and serum globulin were measured by the method of Robinson *et al.* (6). Plasma volume was ascertained by the technique of Greggerson and Stewart (7). The number of days of collection in each case is indicated in accompanying table.

RESULTS

Nitrogen balance studies were made in the five subjects, each of whom was fed a constant diet calculated and analyzed to contain 1.3 gm. of protein per kg. body weight, per day. After each individual had taken the diet satisfactorily for at least 9 days, his daily nitrogen excretion was measured. In the next 8 to 42 days these measurements indicated that in four of the subjects an average daily nitrogen retention of from 0.85 to 4.8 gm. had occurred. In the same preliminary period, the fifth subject, a normal man, had an average negative nitrogen balance of 1.8 gm. per day.

The daily intramuscular injection of 50 mg.

[1] To be presented before the Twenty-Seventh Annual Meeting of the Association for the Study of Internal Secretions, Chicago, Illinois, June 13, 1944.

[2] The fat and protein content of these diets was checked repeatedly by chemical analyses. The carbohydrate fraction was ascertained from standard dietary tables.

of testosterone propionate[3] for from 7 to 9 days to one of the normal men and to the three patients with gastric cancer increased the daily average nitrogen retention by from 1.5 to 3.75 gm. Despite the fact that during the administration of the steroid the total nitrogen retention was equivalent to from 201 to 276 gm. of protein, the total amounts of albumin and globulin in the serum decreased in all instances. ceived intramuscularly 90 mg. of testosterone[4] per day instead of the testosterone propionate. In a 42-day basal period his average daily nitrogen balance had been −1.8 gm., but during the first 30 days of the steroid administration this increased to +2.1 gm. Despite this sharp nitrogen retention (equivalent to a total of 392 gm. of protein), both the concentration of and total amounts of albumin and globulin in

EFFECTS OF TESTOSTERONE AND ESTOSTERONE PROPIONATE ON NITROGEN METABOLISM

Subject	Period	Days	Average Nitrogen Balance gm./day	Protein Fabrication in Period gm.	Concentration of Serum		Plasma Volume liters	Total Circulating	
					Albumin gm. %	Globulin gm. %		Globulin gm.	Albumin gm.
J. C.	Basal	9	4.8	270	5.5	1.7	2.7	137.5	42.5
Gastric carcinoma	Testosterone Propionate	7	6.3	276	4.0	0.8	2.75	109.0	21.0
	50 mg.	6	7.1	269	4.9	0.9	2.5	122.5	22.5
L. T.	Basal	14	4.1	355	4.6	0.6	2.5	115.0	15.0
Gastric carcinoma	Testosterone Propionate 50 mg.	7	6.0	262.5	4.75	0.3	2.3	109.0	7.0
J. K.	Basal	8	0.85	42.5	4.6	2.05	2.5	115.0	51.0
Gastric carcinoma	Testosterone Propionate	7	4.6	201	4.4	1.5	2.4	106.0	36.0
	50 mg.	4	5.85	146	4.0	2.95	2.2	88.0	65.0
V. F.	Basal	12	1.65	124	5.2	1.5	3.3	172.0	49.0
Normal male	Testosterone Propionate	9	4.3	232	5.1	1.2	3.3	168.0	40.0
	50 mg.	6	4.2	158	5.9	0.9	3.85	227.0	35.0
G. C.	Basal	42	−1.8	−473	5.7	1.0	2.7	154.0	27.0
Normal male	Testosterone 90 mg.	30	2.1	392	5.3	0.4	2.7	143.0	11.0
		18	1.0	112	6.6	1.1	3.2	211.0	35.0

Likewise, the concentration of serum albumin decreased in three individuals and the concentration of serum globulin decreased in all (see table).

In the one normal subject and in two of the three patients with gastric cancer, the administration of testosterone propionate was continued for from 4 to 6 days longer. In this period the daily average amount of nitrogen retained was increased by from 2.3 to 5.0 gm. above that in the basal period. The concentration and total amount of circulating albumin increased significantly in two subjects and were reduced further in one. The concentration of and total amount of circulating globulin increased in one, did not significantly change in another and further decreased in the third individual.

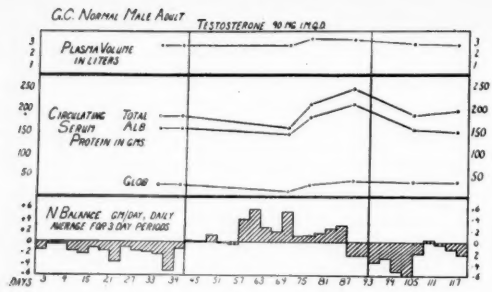
The fifth subject studied, a normal man, received the serum decreased. In the next 18 days the administration of the hormone induced an average nitrogen retention of only + 1.0 gm. per day but at the end of this interval both the concentration of and total amount of serum albumin and serum globulin had risen sharply.

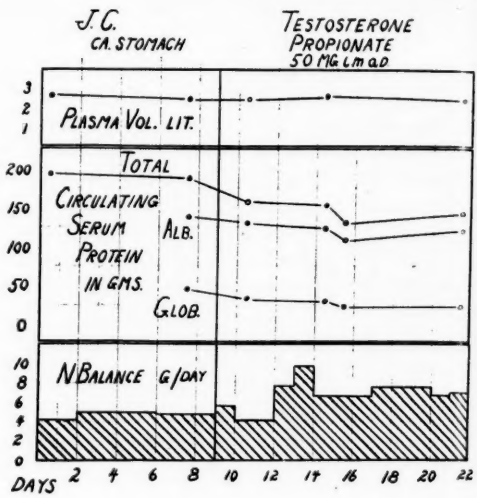
COMMENT

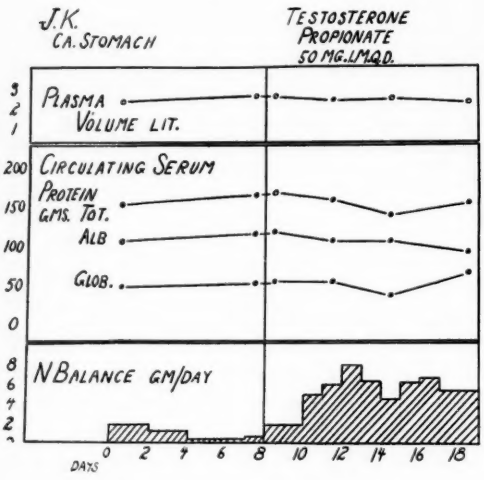
The results presented indicate that the administration of testosterone or its propionate at first induces both an absolute and relative hypoproteinemia. The decrease of serum protein takes place despite the fact that nitrogen is retained. This observation would suggest that not only is the retained nitrogen at first diverted entirely to tissue-protein fabrication but also that tissue protein is formed at the expense of serum protein. Whether the hormone administration initially inhibits serum-

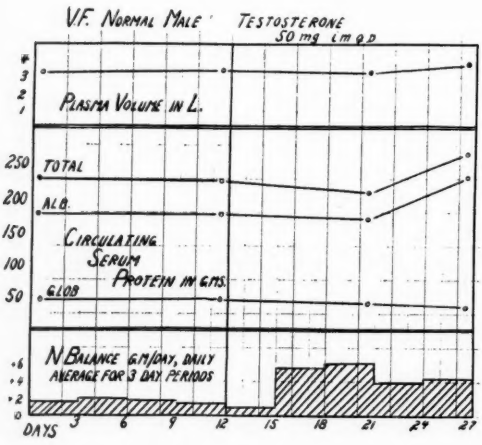
[3] The testosterone proportionate used was that of The Schering Corporation, Bloomfield, N. J.

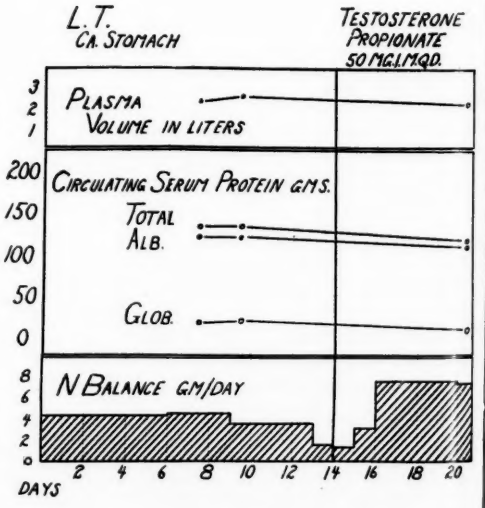
[4] The testosterone was kindly provided by Schering and Company, Bloomfield, New Jersey.











protein formation or induces its conversion to tissue protein cannot be determined from the data at hand. It would appear, however, that neither testosterone nor its propionate would be useful to induce a rapid remission of hypoproteinemic states. Moreover, even the continued use of the steroids resulted in a significant increase of circulating protein above the base levels in only two of four instances, but this lack of uniform response may have

been due to the relatively short period of hormone administration.

SUMMARY

The parenteral administration of testosterone to a normal man and of testosterone propionate to a normal man and to three patients with gastric cancer induced significant nitrogen retention.

Despite the induction of nitrogen retention, the total amounts of circulating protein of all five subjects at first decreased. During this period it is possible either that tissue protein is former from circulating protein or that the administration of the hormones inhibits serum-protein fabrication.

REFERENCES

1. KENYON, A. T.: Conference on Bone and Wound Healing. Second Meeting. 61–70. 1942.
2. ARIEL, I. M., J. C. ABELS, G. T. PACK AND C. P. RHOADS: Metabolic studies in patients with cancer of the gastro-intestinal tract. XI. Postoperative hypoproteinemia and relationship of serum protein fall to urinary nitrogen excretion. *Surg., Gynec., & Obst.* 77: 16. 1943.
3. REKERS, P. E., J. C. ABELS AND C. P. RHOADS: Metabolic studies in patients with cancer of the gastro-intestinal tract. IV. Fat metabolism, a method of study. *J. Clin. Invest.* 22: 243. 1943.
4. PETERS, J., AND D. D. VAN SLYKE: Quantitative Clinical Chemistry. Vol. 1. p. 531. Williams & Wilkins. (Baltimore) (1931).
5. VAN SLYKE, D. D., I. H. PAGE AND E. KIRK: A manometric micro method for determination of carbon and organic compounds. *J. Biol. Chem.* 102: 635. 1933.
6. ROBINSON, H. W., J. W. PRICE, L. C. A. HOGDEN: The estimation of albumin and globulin in serum. *J. Biol. Chem.* 120: 481. 1932.
7. GREGERSON, M. I., AND J. D. STEWART: Simultaneous determination of the plasma volume and the "available fluid" volume with sodium thiocyanate. *Am. J. Physiol.* 125: 142. 1939.

The Excretion of Sodium Pregnanediol Glucuronidate in the Urine Following the Oral Administration of Anhydro-Hydroxy-Progesterone and Progesterone to Patients with Secondary Amenorrhea[1]

WILLARD M. ALLEN, M.D., ELLENMAE VIERGIVER, PH.D., AND SAMUEL D. SOULE, M.D.

From the Department of Obstetrics and Gynecology, Washington University School of Medicine, St. Louis, Missouri

THE DISCOVERY by Venning, Henry and Browne (1937-a) that sodium pregnanediol glucuronidate appears in the urine during the normal menstrual cycle in highest amounts at the time when the corpus luteum is known to be flourishing indirectly indicates that pregnanediol is the excreted form of progesterone. Its presence in the urine in large amounts during pregnancy (Odell and Marrian, 1936; Venning, Henry and Browne, 1937-b; Wilson and Randall, 1938; Backman, Leekley and Hirshman, 1940; Hain, 1940; Smith and Smith, 1940; and, Astwood and Jones, 1941), even when both ovaries have been removed (Jones and Weil, 1938; Young, 1941), also suggests that the placenta, or possibly the fetus, produces progesterone during pregnancy. These observations, coupled with the fact that progesterone can be made from pregnanediol (Butenandt and Schmidt, 1934), support the contention that the presence of pregnanediol in the urine indicates the production somewhere in the body of progesterone. It is quite possible, however, that other compounds closely related to progesterone, such as hormones of the adrenal cortex, may also appear in the urine as pregnanediol.

Studies have already been made of the excretion of pregnanediol in both men and women following the intramuscular injection of progesterone. The results have shown that from 0 to 46 per cent of the amount injected appears in the urine in either sex as sodium pregnanediol glucuronidate (Hamblen, 1940; Hamblen, Cuyler and Hirst, 1940; Buxton, 1940; Buxton and Westphal, 1939; Venning and Browne, 1938; 1940; Jones and TeLinde, 1941; Hamblen, Cuyler, Powell, Ashley and Baptist, 1939). The fate of the remainder is obscure at the present time.

The effectiveness of progesterone, and of the natural estrogens and androgens, is markedly reduced when taken orally. A considerable amount of work done by various investigators indicates that this reduction in activity is due probably to destruction of the compounds by the liver. Only when certain changes are made in the molecule of the natural estrogens, androgens and progesterone is the activity sufficiently enhanced to make oral therapy practical.

[1] To be presented before the Twenty-Seventh Annual Meeting of the Association for the Study of Internal Secretions, Chicago, Illinois, June 12, 1944.

The only compound thus far available which has much progestational action when taken orally is anhydro-hydroxy-progesterone (ethinyl testosterone; pregneninolone) (Inhoffen and Hohlweg, 1938). This compound when taken by mouth is known to produce most of the physiological actions of progesterone providing an adequate amount is given. It produces progestational changes in the uterus of the castrated rabbit and will maintain the embryos (Courrier and Kehl, 1938). It induces sexual receptivity in the estrogen-stimulated, castrated guinea pig (Soderwall, 1940). It produces progestational changes in the uterus followed by withdrawal-bleeding in castrated and menopausal women after suitable priming with estrogen (Salmon, Walter and Geist, 1939; Neustaedter, 1941). It has been found effective in the treatment of functional uterine bleeding (Allen and Heckel, 1942) and in secondary amenorrhea (Zondek and Rozin, 1940; Allen and Soule, 1943). The amount required to produce these effects is much greater than the amount of progesterone needed when the latter is given intramuscularly but it is nevertheless a very useful substitute for progesterone since it can be given by mouth.

In view of the clinical promise of this compound a study was made of the excretion of the compound after oral administration in several patients with secondary and primary amenorrhea[2] at a time when it was thought that there would be no fluctuation in the appearance of pregnanediol in the urine. A total of seven studies extending over a period of several months was made in five different cases. Two short observations were made. One patient was given 500 mg. of anhydro-hydroxy-progesterone[3] by mouth in a single day and the urine collected two days before the therapy and for four subsequent days. This preliminary study indicated that a conjugated compound, presumably sodium pregnanediol glucuronidate, appeared in the urine in measurable amounts after the administration of the compound. In view of this observation a more careful study was planned. Each patient was given 200 mg. per day orally since it was known from previous observations that this amount was adequate to produce stimulation of the uterus and withdrawal-bleeding in many cases of secondary amenorrhea and in some cases of primary amenorrhea.

The urine was collected in 24-hour samples under 300 cc. of normal butyl alcohol in a large bottle. The patient was instructed to transfer the urine to the bottle containing the butyl alcohol after each voiding and immediately to shake the bottle vigorously. This method is fairly satisfactory and surely prevents hydrolysis of at least 80 per cent of the conjugated material. Other studies in this laboratory have shown that there is no de-conjugation of the compound when it is present in the butyl alcohol and also that about 80 per cent appears in the butyl alcohol phase after one extraction (Woolf, Viergiver and Allen, 1942). Twenty-four-hour specimens of urine were obtained daily for a period of two to three days before the administration of the compound, throughout the administration of the compound, and for a period of from five to seven days after the discontinuation of therapy.

The urine specimens were received in the laboratory within a few days of the time of collection. At this time the butyl alcohol phase was increased wherever necessary to make it equivalent to one-third of the volume of the urine. After further shaking and settling, the butyl alcohol was syphoned off and the urine further extracted two times with one-third volume of butyl alcohol. The three butyl alcohol fractions were then combined and made up to a constant volume and three-fifths of the total used for the determination of sodium pregnanediol glucuronidate. This aliquot of butyl alcohol was boiled to dryness, the residue dissolved in one-tenth normal sodium hydroxide, and the sodium hydroxide phase extracted three times with butyl alcohol. The butyl alcohol phase from this extraction is known to contain virtually all of the sodium pregnanediol glucuronidate. This was further processed, according to the method described by Allen and Viergiver (1941), the final determinations being made by determining the amount of glucuronic acid present in the conjugated com-

[2] The cases listed in this paper as *1, 2, 3, 4, 5* were the ones listed in the paper by Allen and Soule (1943) as *21, 17, 12, 1* and *11*, respectively.

[3] The authors wish to thank the Schering Corporation, Bloomfield, New Jersey, for the progesterone and anhydro-hydroxy-progesterone used in this investigation.

pound. This method does not identify the sodium pregnanediol glucuronidate as satisfactorily as the method of Venning and Browne since melting points are not made and the pregnanediol is not actually isolated. The relative values, however, are certainly significant and indicate fairly accurately the amount of the compound excreted in the urine.

The remaining two-fifths of the butyl alcohol fraction was studied for its content of 17-ketosteroids and estrogens. This butyl alcohol fraction was boiled to dryness, the residue dissolved in water and the aqueous solution extracted with ether, thereby extracting the free estrogens and androgens. The aqueous phase was then acidified and hydrolyzed for 30 minutes by boiling after which it was extracted with ether. The estrogens and androgens were separated from the ethereal phase according to the method of Bachman and Pettit (1941). The ketosteroids from both the free and the hydrolyzed fractions were then determined using meta-dinitro-benzene as the reagent according to the method described by Holtorff and Koch (1940). The estrogen fraction was separated into estrone and estriol and the estrogens determined colorimetrically by a modification of the Kober test currently in use in this laboratory which utilizes the absorption band at 450$\mu\mu$ produced by treatment of estrone and estriol with concentrated sulfuric acid.

Since the procedure for the extraction of sodium pregnanediol glucuronidate from the urine does not necessarily extract all the ketosteroid from the urine, the urine was further processed after it had been extracted with butyl alcohol by hydrolyzing with hydrochloric acid. The urine was then extracted with ether and the ethereal fraction further separated into estrogens and androgens, determination of estrogens and androgens being made on these fractions in the same manner as in the butyl alcohol fractions.

URINARY EXCRETION OF SODIUM PREGNANEDIOL GLUCURONIDATE FOLLOWING ORAL ADMINISTRATION OF ANHYDRO-HYDROXY-PROGESTERONE (milligrams per day)

Days	3	2	1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Case 1	11	19	19	47	53	47	37	32	36	14	19							
				600 mg.														
Case 2		13	5	17	29	27	31	33	20	22								
				600 mg.						Bleeding								
Case 3a-		8	3	18	29	25	15											
				500														
Case 3-b		5	5	10	17	27	33	37	31	33	26	24	16	13	8	8	7	7
				200×6=1200 mg.									Bleeding					
Case 3-c[1]	11	14	14	38	46	43	51	47	53	43	23	15	9	4				
				200×6=1200 mg.														
Case 4		34	33	15	29	72	37	51	59	55	53	57	32	27				
				200×6=1200 mg.														
Case 5	33	24	38	49	54	64	42	52	46	44	50	44	18	20				
				200×6=1200 mg.									Bleeding					

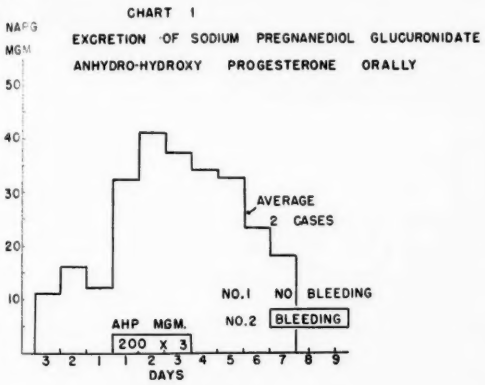
Amounts given are indicated in brackets.
[1] Progesterone given.

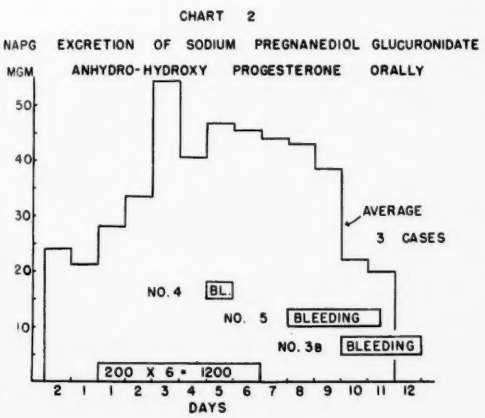
RESULTS AND DISCUSSION

It was found in all cases that there was an increase in the sodium pregnanediol glucuronidate following the administration of 200 or more millligrams per day of anhydro-hydroxy-progesterone. The results are tabulated in the accompanying table. In *Case 3a*, for example, virtually none of the complex was present in the urine prior to the administration of the anhydro-hydroxy-progesterone. Following the administration of a single dose of 500 mg., a maximum of 29 mg. of the conjugated compound was present in the urine the following day. Even on the third day after therapy the level was still twice that present before therapy. In the two cases receiving 200 mg. per day for three days, the maximal level was reached on the second day of therapy. In *Case 2*, bleeding was produced by 200 mg. per day

for three days. Three studies were carried out in which 200 mg. per day was given for a period of six days. In two of these cases withdrawal-bleeding was produced. The production of bleeding in these cases of long-standing amenorrhea establishes the physiological activity of the material given.

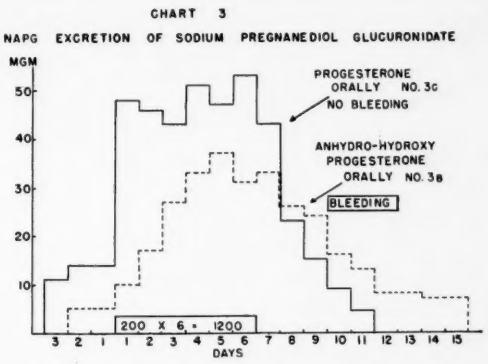
The results have been averaged and recorded in charts 1 and 2. Chart 1 shows the average excretion per day of sodium pregnanediol glucuronidate following the administration of 200 mg. of the anhydro-hydroxy-progesterone daily for three days. It is seen from the study of this chart that there is a prompt increase in sodium





pregnanediol glucuronidate appearing in the urine on the first day of therapy and a somewhat greater amount on the second day of therapy. Following this there is a little change throughout the remainder of therapy and for the first two days after therapy has been discontinued. Then there is a rapid fall to approximately the level present before medication was begun.

In chart 2 is shown the average of the observations on three cases receiving 200 mg. per day for six days. The average level prior to therapy in these three cases is somewhat higher due to the fact that two of these particular



cases seemed to have high levels in the absence of any therapy. All cases, however, showed an increase about as soon as therapy was begun. It is noteworthy in this series of experiments also that there was very little decline in the amount of material appearing in the urine for a period of three days after the therapy was discontinued. In two of these three cases menstrual periods occurred following cessation of therapy. In one case bleeding was noted for one day while therapy was in progress.

After these observations had been made with anhydro-hydroxy-progesterone it was thought that equally interesting observations might be made with progesterone when given in similar amounts. Consequently, one of the cases was given 200 mg. of progesterone orally per day for a period of six days and the amount of sodium pregnanediol glucuronidate excreted in the urine measured in the same way as in the other cases. This study proved to be of considerable interest. Collections were carried out very satisfactorily by this patient and the urine volumes were relatively constant. It will be noticed from chart 3 that the first day of therapy the amount excreted in the urine was considerably higher than that seen on the first day of therapy with anhydro-hydroxy-pro-

gesterone. In fact, on the first day the level was virtually as high as it was on any subsequent day of medication. Also on the first day after therapy had been discontinued, the level still remained fairly high, but by the second day it was fairly low, almost as low as before therapy had been begun and by the third day, the level had decreased to the pre-therapy point. If this one observation be typical, it indicates that progesterone is metabolized considerably more rapidly than anhydro-hydroxy-progesterone and it suggests that progesterone is inactive when taken orally because it is too rapidly converted to pregnanediol, and conversely, that anhydro-hydroxy-progesterone may be active by mouth because it is not so rapidly converted to pregnanediol.

The maximal levels of excretion following progesterone and anhydro-hydroxy-progesterone in equivalent dose are about the same. In each case the excretion is approximately 50 mg. of conjugated compound per day when 200 mg. is taken by mouth. The progesterone, when given orally, appeared to be inactive, or at least withdrawal-bleeding did not occur with this particular dose, whereas the same patient did have withdrawal-bleeding when an equivalent dose of anhydro-hydroxy-progesterone was given.

These observations on the excretion of sodium pregnanediol glucuronidate following the oral administration of anhydro-hydroxy-progesterone and progesterone indicate that these compounds do appear in the urine in a conjugated form, presumably sodium pregnanediol glucuronidate. It should be emphasized, however, that the pregnanediol was not actually isolated in this study, and it is only by supposition that we concluded that the compound measured is actually pregnanediol. It is possible, of course, that it may be a related steroid which is conjugated with glucuronic acid in the same manner as pregnanediol is conjugated.

The study of the amount of ketosteroid excreted following the administration of progesterone and anhydro-hydroxy-progesterone indicates that there was no increased production of ketosteroids. The values obtained before therapy, during therapy, and after therapy showed no fluctuation beyond the normal limits of variation. Treatment of this fraction, however, with concentrated sulfuric acid (Talbot, Berman, MacLachlan and Wolfe, 1941) did indicate an increase in a neutral steroid, presumably pregnanediol, which was approximately equivalent to the amount obtained by the measurement of the glucuronic acid present in the sodium pregnanediol glucuronidate fraction.

Determination of estrogen by the Kober test indicated no increase during therapy or after therapy. In fact, no estrogen was measurable by this test as it is being carried out in this laboratory at the present time. This is not surprising since anhydro-hydroxy-progesterone is known to have no estrogenic action in the menopausal woman (Salmon and Geist, 1940).

The results obtained in this study do not agree with those previously obtained by others. Goldberg and Hardegger (1941) observed no increase in the excretion of pregnanediol (or of 17-ketosteroid) following the administration of 1,000 mg. in each of two women who had a complete hysterectomy and bilateral salpingo-oöphorectomy. This suggests, although it does not prove, that the compound determined in this study may not be sodium pregnanediol glucuronidate but some related steroid which is conjugated with glucuronic acid. Hamblen, Cuyler and Hirst (1940) also found no increase in the excretion of sodium pregnanediol glucuronidate during the oral administration of 40 mg. per day over a period of eight days. The amount given, however, may have been insufficient to give a measurable increase in the amount excreted since only about ten per cent of that given appears to be recoverable in the urine.

SUMMARY

The oral administration of anhydro-hydroxy-progesterone results in the excretion in the urine of a conjugated steroid. Approximately ten per cent of the total quantity ingested is recoverable in the urine as a conjugated steroid, presumable sodium pregnanediol glucuronidate. The amount of sodium pregnanediol glucuronidate recovered in the urine is approximately the same when progesterone is taken as when anhydro-hydroxy-progesterone is given although the former compound appears to be inactive.

REFERENCES

ALLEN, W. M., AND G. P. HECKEL: *Am. J. Obst. & Gynec.* 44: 984. 1942.

ALLEN, W. M., AND S. D. SOULE: *South. Med. J.* 36: 415. 1943.

ALLEN, W. M., AND ELLENMAE VIERGIVER: *J. Biol. Chem.* 141: 837. 1941.

ASTWOOD, E. B., AND G. E. SEEGAR JONES: *J. Biol. Chem.* 137: 397. 1941.

BACHMAN, C., D. LEEKLEY AND H. HIRSCHMANN: *J. Clin. Investigation* 19: 801. 1940.

BACHMAN, C., AND D. S. PETTIT: *J. Biol. Chem.* 138: 689. 1941.

BROWNE, J. S. L., J. S. HENRY AND E. H. VENNING: *J. Clin. Investigation* 16: 678 1937 (b).

BUXTON, C. L.: *Am. J. Obst. and Gynec.* 40: 202. 1940.

BUXTON, C. L., AND U. WESTPHAL: *Proc. Soc. Exper. Biol. & Med.* 41: 284. 1939.

BUTENANDT, A., AND J. SCHMIDT: *Ber. dtsch. chem. Ges.* 67: 1901. 1934.

COURRIER, R., AND R. KEHL: *Compt. rend. Soc. de biol.* 128: 188. 1938.

GOLDBERG, M. W., AND E. HARDEGGER: *Schweiz. med. Wchnschr.* 22: 1041. 1941.

HAIN, A. M.: *Endocrinol.* 2: 104. 1940.

HAMBLEN, E. C.: *Endocrinol.* 27: 33. 1940.

HAMBLEN, E. C., W. K. CUYLER AND D. V. HIRST: *Endocrinol.* 27: 35. 1940.

HAMBLEN, E. C., W. K. CUYLER AND D. V. HIRST: *Endocrinology* 27: 172. 1940.

HAMBLEN, E. C., W. K. CUYLER AND D. V. HIRST: *Endocrinol.* 25: 13. 1939.

HOLTORFF, A. F., AND F. C. KOCH: *J. Biol. Chem.* 135: 377. 1940.

INHOFFEN, H. H., AND W. HOHLWEG: *Die Naturwissenschaften.* 26: 96. 1938.

JONES, G. E., R. W. TELINDE: *Am. J. Obst. & Gynec.* 41: 682. 1941.

JONES, H. W. AND P. G. WEIL: *J. Am. Med. Assn.*, 111: 519. 1938.

NEUSTAEDTER, T.: *Am. J. Obst. & Gynec.* 24: 86. 1941.

ODELL, A. D., AND G. F. MARRIAN: *Biochem. J.* 30: 1533. 1936.

SALMON, N. J., AND S. H. GEIST: *Proc. Soc. Exper. Biol. & Med.* 45: 522. 1940.

SALMON, N. J., R. I. WALTER AND S. H. GEIST: *Proc. Soc. Exper. Biol. & Med.* 40: 252. 1939.

SMITH, G. V. S., AND O. W. SMITH: *Am. J. Obst. & Gynec.* 39: 405. 1940.

SODERWALL, ARNOLD L.: *Endocrinol.* 27: 841. 1940.

TALBOT, N. B., R. A. BERMAN, E. A. MACLACHLAN AND J. K. WOLFE: *J. Clin. Endocrinol.* 1: 668. 1941.

VENNING, E. H., AND J. S. L. BROWNE: *Am. J. Physiol.* 123: 209. 1938.

VENNING, E. H., AND J. S. L. BROWNE: *Endocrinol.* 27: 707. 1940.

VENNING, E. H., J. S. HENRY AND J. S. L. BROWNE: *Canad. Med. Assn. J.* 36: 83. 1937 (a).

WILSON, R. B., AND L. M. RANDALL: *Proc. Staff Meet. Mayo Clinic*, 13: 813. 1938.

WOOLF, R. B., ELLENMAE VIERGIVER AND W. M. ALLEN: *J. Biol. Chem.* 146: 323. 1942.

YOUNG, W. R.: *Illinois M. J.* 80: 132. 1941.

ZONDEK, B., AND S. ROZIN: *Am. J. Obst. and Gynec.* 40: 391. 1940.

Optimal Requirements for Adrenal Cortical Hormones as Observed in Adrenalectomized Animals

A Brief Review

DWIGHT J. INGLE, PH.D.

From the Research Laboratories of the Upjohn Company, Kalamazoo, Mich.

IN TREATING adrenal cortical insufficiency it is desirable to ascertain the level of replacement therapy required to substitute completely for the functional activity of normal adrenal cortices. It is common to judge either the animal or the patient as physiologically normal in respect to adrenal cortical function whenever life is maintained and the proportions of water and crystalloids of the blood are within normal limits. There is ample evidence that the requirements for complete replacement therapy by cortical hormones are far greater than is commonly judged to be the case on the basis of these criteria.

The purpose of this paper is to consider briefly a few of the laboratory studies relative to this problem. For the reason that the experience of the writer is limited to the laboratory, discussion of therapy in patients is omitted.

Ingle and Higgins (1) observed that when one adrenal gland of the rat was enucleated and the contralateral gland was removed there was rapid regeneration of the enucleated gland from its capsule. However, when one gland was enucleated and the contralateral gland was left intact regeneration was fully suppressed. This provided a new criterion for estimating the amount of cortical extract required to replace the functional activity of one intact adrenal gland, i.e., how much cortical extract is required to suppress regeneration processes as effectively as one intact adrenal gland? An adrenal cortical extract was used which was known to maintain life and normal proportions of water and crystalloids in the blood of adrenalectomized rats in amounts of 0.3 cc. (each cc. derived from 75 gm. whole beef adrenal gland) daily. The smallest amount of cortical extract which suppressed regeneration of the enucleated gland as effectively as would the presence of the contralateral gland was found to be 5 cc. (375 gm. gland equivalent) daily.

It was shown by Cartland and Kuizenga (2) that extracts of beef adrenal glands (40 gm. of gland per cc.) would maintain the life and growth of young, adrenalectomized rats in amounts of 0.12 to 0.25 cc. daily and when tested in adrenalectomized dogs would maintain life and a normal level of non-protein nitrogen in amounts not greater than 0.25 cc. daily per dog. Long and Lukens (3, 4) found that pancreatic diabetes could be alleviated by the removal of the adrenal cortices but that the diabetic state could not be reinduced by the administration of cortical extracts considerably in excess of the amounts sufficient to maintain life and normal proportions of water and crystalloids in the blood. Further investigations by Lukens and Dohan (5) and by Long, Katzin and Fry (6) have shown that only very large amounts of cortical extracts could replace the functional activity of the adrenal cortices by reinducing glycosuria of the intensity which characterized depancreatized animals having the adrenal glands intact. For the dog (5) the daily effective dose was 10 to 40 cc. of adrenal

cortex extract (Upjohn) and for the rat (6) the daily effective dose was 5 to 10 cc. daily of the same preparation.

Although most investigators of adrenal cortical functions have recognized that the dosage of cortical extract must be increased when the adrenalectomized animal is subjected to stress, the really great discrepancy between the minimal effective dose when other conditions favoring survival are optimal and the minimal effective dose during stress has not been universally appreciated in either the laboratory or the clinic. In the extensive studies of this problem carried out by Swingle and his associates (7, 8) doses of cortical extract of 0.3 to 0.5 cc. per kg. of dog were used. The extract represented 50 gm. of beef adrenal gland per cc. This dosage was adequate to maintain adrenalectomized dogs entirely free from symptoms of cortical insufficiency. The dogs were described as normal in appearance, behavior and appetite. The blood pressure, pulse, serum electrolytes and water, blood sugar and urea nitrogen were normal. The water balance and excretion of electrolytes were normal. This dosage level did not maintain normal resistance for a degree of trauma easily tolerated by normal dogs caused these animals to develop shock and a circulatory collapse. The amount of cortical extract used to maintain resistance to stress or to bring about recovery of adrenalectomized dogs from shock was 3 cc. per kg. per day.

In a study of the effect of adrenal cortical extract on the response of adrenalectomized rats to intraperitoneal injections of an isotonic glucose solution, Remington (9) found that it required 6 cc. of cortical extract (40 gm. beef adrenal per cc.), or approximately twenty-four times the minimum life-maintenance dose, to prevent fatal collapse in this experiment.

Although only a small fragment of an adrenal gland is required to maintain the life of experimental animals when conditions for survival are optimal, the surgically reduced gland will not maintain normal resistance to stress. It was shown by Horvath, Hitchcock and Hartman (10) that the unilaterally adrenalectomized rat has less than normal resistance to cold; by Remington (9) that the unilaterally adrenalectomized rat has less than normal resistance to the interperitoneal injection of glucose; and by Ingle (11) that the unilaterally adrenalectomized rat performs less than normal amounts of work.

A study carried out by Vogt (12) may prove to be of great importance in adrenal physiology. This investigator attempted to estimate the amounts of cortical hormones secreted by the adrenal cortex by collecting blood from the adrenal veins and assaying the serum by the Selye-Schenker test (13). The results indicated that the adrenal cortices of the experimental animals studied—the dog, cat, pig, goat and rabbit—secreted very large amounts of cortical hormones. For example, it was estimated that the adrenal cortices of a 10-kg. dog can secrete in 24 hours the equivalent of 230 cc. of an adrenal cortical extract representing 17,300 gm. of beef adrenal gland. Although this study included several well-considered controls which were intended to insure the validity of this direct estimation of hormone output, acceptance of these conclusions can be accorded only after independent confirmation based upon separation of the hormones from the other constituents of blood serum and testing by other methods of assay.

As shown by the results of the few representative studies reviewed here the usual life-maintenance doses of cortical extracts fail to maintain normal carbohydrate metabolism and also normal resistance to stress. It is probable that these two changes from normal are menifestations of the same fundamental deficiency. It has been established (14–16) that the C_{11} oxygenated cortical steroids (corticosterone, 11-dehydrocorticosterone, 17-hydroxycorticosterone and 17-hydroxy-11-dehydrocorticosterone) are much more effective in maintaining resistance and normal carbohydrate metabolism in adrenalectomized animals than are such preparations as 11-desoxycorticosterone and the amorphous fraction (17) which are highly effective in maintaining life when conditions for survival are optimal. When extracts of beef adrenal glands are assayed for activity characteristic of the C_{11} oxygenated steroids it is found to be low. Kuizenga *et al.* (18) have found by use of a work test (19) that beef adrenal extracts have, on the average, an activity equivalent to about 0.2 mg. of 17-hydroxy-11-dehydrocorticosterone per cc.

(each cc. derived from 40 gm. of gland). Independent studies by Wick (20) and by Thayer (21)using a glycogenic test have confirmed this finding. Isolation studies (17, 22) have also shown that the amount of C_{11} oxygenated steroids in beef adrenal glands is small but that there can be separated from the known compounds an amorphous, chemically unidentified mixture of compounds which is highly active in respect to its ability to maintain life under optimal conditions but which is weak in its effect on resistance and carbohydrate metabolism.

SUMMARY

A review of some of the more relevant laboratory investigations is offered. It seems probable that the findings on the chemistry of adrenal cortical extracts provide the explanation for the consistent observation that small amounts of beef adrenal extracts will maintain life in adrenalectomized animals when conditions for survival are optimal but relatively massive doses are required to maintain normal resistance to stress.

REFERENCES

1. INGLE, D. J., AND G. M. HIGGINS: *Am. J. Med. Sci.* 196: 232. 1938.
2. CARTLAND, G. F., AND M. H. KUIZENGA: *Am. J. Physiol.* 117: 678. 1936.
3. LONG, C. N. H., AND F. D. W. LUKENS: *J. Exp. Med.* 63: 465. 1936.
4. LONG, C. N. H.: *Cold Spring Harbor Symposia on Quantitative Biology.* 5: 344. 1937.
5. LUKENS, F. D. W., AND F. C. DOHAN: *Endocrinol.* 22: 51. 1938.
6. LONG, C. N. H., B. KATZIN AND E. G. FRY: *Endocrinol.* 26: 309. 1940.
7. SWINGLE, W. W., AND W. M. PARKINS: *Am. J. Physiol.* 111: 426. 1935.
8. SWINGLE, W. W., W. M. PARKINS, A. R. TAYLOR AND H. W. HAYS: *Am. J. Physiol.* 124: 22. 1938.
9. REMINGTON, J. W.: *Endocrinol.* 32: 129. 1943.
10. HORVATH, S. M., F. A. HITCHCOCK AND F. A. HARTMAN: *Am. J. Physiol.* 121: 178. 1938.
11. INGLE, D. J.: *Endocrinol.* 26: 478. 1940.
12. VOGT, M.: *J. Physiol.* 102: 341. 1943.
13. SELYE, H., AND V. SCHENKER: *Proc. Soc. Exper. Biol. & Med.* 39: 518. 1938.
14. LONG, C. N. H.: *Endocrinol.* 30: 870. 1942.
15. INGLE, D. J.: *Endocrinol.* 31: 419. 1942.
16. SWINGLE, W. W., AND J. W. REMINGTON: *Physiol. Rev.* 24: 89. 1944.
17. KENDALL, E. C.: *Endocrinol.* 30: 853. 1942.
18. KUIZENGA, M. H., A. N. WICK, D. J. INGLE, J. W. NELSON AND C. F. CARTLAND: *J. Biol. Chem.* 147: 561. 1943.
19. INGLE, D. J.: *Endocrinol.* 34: 191. 1944.
20. WICK, A. N.: Personal communication.
21. THAYER, S. A.: Personal communication.
22. KUIZENGA, M. H.: *Gibson Island Symposium on Hormones.* In press

Some Recent Advances in Experimental Endocrinology

EDWARD W. DEMPSEY, PH.D.

From the Department of Anatomy, of the Harvard Medical School, Boston, Massachusetts

THE CURRENT emergency has severely restricted research in the endocrine field, partly by new and unexpected demands on the time of investigators, partly by reduction in personnel and partly by the lack of availability of materials. Furthermore, the last five years have closed an era characterized by the description of a multitude of endocrine products and their effects and have opened a new era during which the analytical method seems destined to become more and more fruitful. Perhaps, therefore, it is opportune to review some of the results obtained during this transition period for reorientation against the day when the present restrictions are lifted.

PITUITARY

The concept of the anterior pituitary as the master gland of the endocrine system has been maintained as an important, directing influence in the analysis of pituitary function. There now seems no room for reasonable doubt that the pituitary gland elaborates a number of endocrine products. Four of the fractions have been so purified chemically that each moves with a single rate in the Tiselius electrophoresis apparatus. The substances so purified are the thyreotropic, luteinizing or interstitial-cell-stimulating, lactogenic and growth hormones. Furthermore, the follicle-stimulating and adrenotropic hormones have been separated from contaminating principles as judged by biological tests [for references, see (1)]. It may be remarked parenthetically that the criterion of biological purity seems preferable to that of purity as judged by the Tiselius apparatus or any other physical chemical measurement, since on theoretical grounds it is evident that proteins of very different natures may have similar or identical electrophoretic mobilities (2).

The chemical separation of the protein hormones, although a dramatic step forward in our understanding of the biological rôles played by these complex substances, does not completely settle the problem of how and in what form the hormones are secreted by the pituitary. Large though the individual molecules may be, is it not possible they may still represent fragments of still larger molecules elaborated by the gland? In other words, may not the fractions purified by chemical treatment represent the active prosthetic groups of a still larger master molecule? On cytological grounds, one can recognize only two secretory cell types in the anterior pituitary and it is difficult to reconcile this fact with the concept of a multiplicity of anterior lobe hormones. Nevertheless, a study involving the stimulation or depression of the adrenal, thyroid and ovary as a result of experimental modification of the environment in which rats were maintained led to evidence suggesting that the adrenotropic, thyreotropic and gonadotropic hormones, at least, are secreted in physiological independence (3). Consequently, since both chemical and physiological evidences support the concept of many pituitary hormones, it seems necessary to assume that a single cytological cell type is capable of doing more than one thing at a time.

The responsiveness of the endocrine glands to modifications of the external environment, mentioned above, introduces the question of the relationship of the nervous system to the endocrine glands. Exposure to cold or hot en-

vironments alters markedly the size and appearance of the thyroid and adrenal glands (4). Light profoundly modifies reproductive activity in a number of species (5). Moreover, this effect is clearly mediated by the nervous system since enucleation of the eyes or sectioning of the optic nerves abolishes the response (6). A similar neural control of the pituitary is demonstrated in the dependence of ovulation upon the stimulus of copulation in such animals as the rabbit, cat, and ferret. In such animals transection of the pituitary stalk leads to a failure of ovulation after coitus (7), although this operation does not interrupt the reproductive cycle or ovulation in the spontaneously ovulating species as exemplified by the guinea pig (8, 9), rat (10), and man (11).

GONADS

The gonadal hormones have been found to modify sexual behavior profoundly. In subprimate species, gonadectomy leads to an abolition or marked diminution of sex activity. This effect is greater in the female than in the male, since in the latter many instances are known in which copulatory activity may appear even after prepuberal castration. However, in gonadectomized animals of both sexes, reproductive behavior reappears or is quantitatively increased by appropriate treatment with the gonadal hormones (12). Combination treatment with estrogen and progesterone are more effective than estogen alone in inducing female sexual behavior in a number of species (13, 14, 15). It is odd, however, that testosterone has a capacity to increase female sexual behavior not only in the common laboratory animals but in human subjects as well.

The processes and conversions which occur during the metabolism of the steroid hormones have received continuous attention. Considerable practical importance is attached to the demonstration that, in the human subject, progesterone is excreted as pregnandiol glycuronidate (16). This metabolite is easily identifiable in the urine and serves as an indicator of luteal function. Different species apparently metabolize the steroidal substances in different ways, however, since pregnandiol cannot be isolated from the urine of sub-primates.

Evidence from a number of sources indicates that the liver is an important organ for the destruction or detoxification of steroidal hormones. Estrogens exert a prolonged effect after damage to the liver (17), the anesthesia caused by large doses of steroid substances is prolonged after hepatectomy (18), and estrogens are destroyed in vitro by liver brei and by certain micro-organisms (19, 20, 21). On the other hand, studies on the distribution of estrogens between the blood and bile have led to the concept that these hormones accumulate in the entero-hepatic system where they can be destroyed in a leisurely fashion (22).

The relationships between the gonads and the pituitary are now known in considerable detail. The follicle-stimulating hormone induces growth of the ovarian follicle and stimulates spermatogenesis (23). In neither sex does it cause secretion of the gonadal hormones. For the elaboration of estrogen in the female and testosterone in the male, the luteinizing hormone is essential (24). The control of the endocrine activity of the ovary is still further complicated by the fact that a third gonadotropic element, luteotrophin, seems to be necessary for the secretion of progesterone by the formed corpus luteum (25). These hormonal factors wax and wane during the reproductive cycle in a fashion which seems adequately comprehensible except for the question of the stimulus which induces the release of luteinizing hormone antecedent to ovulation. It has been suggested that an increasing concentration of estrogen causes the release of luteinizing hormone by a trigger mechanism (24) and also that the phenomenon is under the control of some nervous influence (7); but neither of these explanations is entirely satisfactory (8).

ADRENAL CORTEX

Continued investigation of steroidal substances isolated from the adrenal cortex has determined the structural formulae of some twenty-eight compounds (26). Not all of these substances have biological effects. Among them, however, are substances which have estrogenic, androgenic, sodium-conserving or carbohydrate-regulating properties. It now is evident that a number of compounds related to progesterone and desoxycorticosterone can prevent the loss of sodium in the urine and re-

pair the electrolytic disequilibrium subsequent to adrenalectomy and Addison's disease (27). On the other hand, the disturbances in carbohydrate metabolism which occur after destruction of the adrenal are not alleviated by these same compounds. Another class of steroids, those containing an oxygen atom at the C_{11} position, is required for the restoration of the carbohydrate metabolism (26). The disturbance may be related to the conversion of protein into carbohydrate (28).

The adrenal glands are remarkably stimulated by exposure to cold or to noxious agents (29). It is not yet clear whether this stimulation results in the increased production of the salt-regulating or carbohydrate-regulating factor, or influences some other unknown function.

THYROID

Two technical advances have led to great progress in the understanding of the metabolism of the thyroid hormone. The first of these is the use of radioactive iodine as a tracer element for the study of the metabolism of iodine by the gland (30, 31, 32). The second concerns the discovery that certain sulfur-containing drugs cause a marked hyperplasia of the thyroid gland (33, 34, 35). An analysis of the factors underlying this remarkable hyperplasia has shown that it is prevented by hypophysectomy or the administration of thyroid hormone and that it is associated with a fall in the basal metabolic rate. The BMR can, however, be restored to normal or supernormal values by the administration of the thyroid hormone concurrently with the antithyroid drug. These facts provide a demonstration that the antithyroid drugs act by inhibiting the formation of the thyroid hormone (33, 34), a concept which is further vindicated by the observation that the iodine content of the gland falls during treatment (36) and that the iodine uptake by the gland is also inhibited by the antithyroid substances (37, 38). Furthermore, the observations provide a method for the determination of the rate of thyroid hormone secretion in the normal animal, since the normal rate may be taken as equivalent to the daily amount of thyroxin necessary to prevent the hyperplasia caused by the antithyroid drugs. Experiments designed along these lines have shown that the rate of secretion is approximately six times as great in rats maintained at freezing temperatures as in animals maintained at 35° C. (39), and that thyroidal activity is greater in the egg-producing breeds of chickens than in the larger breeds raised for meat production (40).

Experiments involving an analysis of the uptake of iodine by the thyroid gland have shown that iodination of organic substances and the formation of thyroxin are both inhibited by the antithyroid drugs (41). These findings are in accord with the demonstration that neither potassium iodide (33, 34) nor diiodotyrosine (39) will substitute for thyroxin in inhibiting the experimental hyperplasia. These facts suggest an enzymatic inhibition by the antithyroid drugs (39, 41) and it has been suggested that the cytochrome system (41) or a peroxidase system (42) is essential in the formation of thyroxin.

PANCREAS

The recent discovery that alloxan, when administered to animals, causes a severe and irreversible diabetes has considerable interest (43). Following administration of a single dose of the drug there is a severe hypoglycemia lasting about 24 hours, followed by a permanent rise in the blood sugar. The hyperglycemia can be controlled by insulin. An investigation of the islands of Langerhans showed that there is an immediate necrosis of the β cells, which in severe cases causes their complete abolition (44). Presumably there is an immediate release of preformed insulin during the early necrosis which causes the intial hypoglycemia. After the store of insulin has been removed, a permanent insulin deficiency results in a permanent diabetes. The effect is of considerable theoretical interest, since alloxan is a naturally occurring product of protein metabolism. There may well be a connection between the alloxan diabetes and the similar destruction of the islands of Langerhans which is induced by prolonged treatment with anterior pituitary extracts (45), since the pituitary hormones are known to alter nitrogen retention and protein metabolism in the animal body.

HISTOCHEMISTRY OF THE ENDOCRINE GLANDS

A number of recent investigations have cen-

tered around the problem of the histological demonstration of various hormones or their secretory antecedents. The adrenal (46), testis (47), ovary (48) and placenta (49) have been investigated, utilizing several histochemical reactions which indicate the presence of steroidal compounds. Thus, the localization of birefringent substances, particularly after treating the sections with digitonin, has provided information because cholesterol and other steroids form spherocrystals and their crystalline digitonides are strongly birefringent (50). The phenylhydrazine reaction, before and after extraction of sections by organic solvents, has yielded further information because many of the biologically active hormones are keto-compounds. Similarly, the Libermann-Burchardt reagents, modified to permit their use in histological sections, produce a colored reaction with unsaturated steroidal substances. Lastly, the fluorescence of the steroids has also been employed as a means of localizing steroidal compounds in mammalian tissues.

The application of some or all these methods to the adrenal, testis, ovary and placenta has shown that substances giving positive reactions are localized in particular regions. In the adrenal, a zone of activity occurs in the outer portion of the zona fasciculata (46). Positive reactions in the testis are obtained only in the interstitial cells (47). The theca interna (but not the granulosa), the corpus luteum and the interstitial tissue contain the reactive substances in the ovary (48). Lastly, positive reactions are associated with the lipoidal droplets in the syncytial layer of the placenta (49).

The application of tests for reducing compounds to the adrenal medulla has shown that substances, the reactions of which are similar to those of adrenalin, are normally present in some cells but not in others (51). Moreover, stimulation of the adrenal by faradization of the splanchnic nerve led to an increase in the amount of reacting substances. This last observation indicates that adrenalin is presumably synthesized on stimulation from some inactive precursor.

Although conventional methods for the histochemical determination of iodine in the thyroid gland have failed or are theoretically unsound (52), two methods which have been recently applied have provided interesting leads for further investigation. Observations on the fluorescence of thyroidal colloid have shown that the fluorescence is preserved by protein precipitants, is diminished or abolished by reagents in which thyroglobulin is soluble, and is abolished by experimental procedures which deplete the iodine content of the thyroid (42). Another method by which the iodine content of the colloid is revealed is the absorption of soft x-rays by the colloid in tissue sections. The colloid becomes transparent to the rays after removal of the iodine from the sections by treatment with acid sodium nitrite (53).

MECHANISM OF ACTION OF HORMONES

As a final comment on the progress of endocrinology during the past five years, it should be pointed out that very little is known of the mechanism by which endocrine substances exert their effects. The usual endocrine procedures, consisting of the production of morphological or metabolic effects after experimental alteration of the endocrine activities, do not lend themselves to analysis of the means by which the ultimate effects are produced. Consequently, it would appear that clues as to the mode of action of the hormones must come from other kinds of experiments. The recent demonstration that natural and synthetic estrogens have in common the property of altering the characteristic reactions of monomolecular protein films (54) provides an interesting lead for future speculation and research.

REFERENCES

1. VAN DYKE, H. B., B. F. CHOW, V. DU VIGNEAUD, H. L. FEVOLD, G. W. IRVING, JR., C. N. H. LONG, T. SHEDLOVSKY AND A. WHITE: Protein hormones of the pituitary body. *Ann. New York Acad. Sci.* 43: 253. 1943.
2. PIRIE, N. W.: The criteria of purity used in the study of large molecules of biological origin. *Biol. Rev.* 15: 377. 1940.
3. DEMPSEY, E. W., AND H. F. SEARLES: Environmental modification of certain endocrine phenomena. *Endocrinol.* 32: 119. 1943.
4. CRAMER, W.: Fever, Heat Regulation, Climate and the Thyroid-Adrenal Apparatus. Longmans, Green and Co., London, 1928.
5. BROWMAN, L. G.: Light in its relation to activity and estrous rhythms in the albino rat. *J. Exper. Zool.* 75: 375. 1937.
6. DEMPSEY, E. W.: Unpublished observations.

7. Brooks, C. McC.: A study of the mechanism whereby coitus excites the ovulation-producing activity of the rabbit's pituitary. *Am. J. Physiol* 121: 157. 1938.
8. Dempsey, E. W.: The relationship between the central nervous system and the reproductive cycle in the female guinea pig. *Am. J. Physiol.* 126: 758. 1939.
9. Dey, F. L.: Evidence of hypothalamic control of gonadotropic functions in the female guinea pig. *Endocrinol.* 33: 75. 1943.
10. Dempsey, E. W., and U. U. Uotila: The effect of pituitary stalk section upon reproductive phenomena in the female rat. *Endocrinol.* 27: 573. 1940.
11. Dandy, W. E.: Section of the human hypophysial stalk. Its relation to diabetes insipidus and hypophysial functions. *J. Am. Med. Assn.* 114: 312. 1940.
12. Leach, F. A.: Analysis of factors involved in the arousal, maintenance and manifestation of sexual excitement in male animals. *Psychomat. Med.* 4: 173. 1942.
13. Dempsey, E. W., R. Hertz and W. C. Young: The experimental induction of oestrus (sexual receptivity) in the normal and ovariectomized guinea pig. *Am. J. Physiol.* 116: 201. 1936.
14. Boling, J. L., and R. J. Blandau: The estrogen-progesterone induction of mating responses in the spayed female rat. *Endocrinol.* 25: 359. 1939.
15. Ring, J. R.: The estrogen-progesterone induction of sexual receptivity in the spayed female mouse. *Endocrinol.* 34: 269. 1944.
16. Venning, E. H., and J. S. L. Browne: A study of the metabolism of crystalline progesterone. *Endocrinol.* 27: 707. 1940.
17. Talbot, N. B.: The inactivation of endogenous estrogen by the liver. *Endocrinol.* 25: 601. 1939.
18. Selye, H.: On the rôle of the liver in the detoxification of steroid hormones and artificial estrogens. *J. Pharmacol. & Exper. Therap.* 71 236. 1941.
19. Zondek, B., and F. Sulman: Inactivation of estrone and diethylstilbestrol by micro-organisms. *Endocrinol.* 33: 204. 1943.
20. Zondek, B., F. Sulman and J. Sklow: Inactivation of stilbestrol by liver in vitro. *Endocrinol.* 33: 333. 1943.
21. Graubard, M., and G. Pincus: Steroid metabolism: Estrogens and phenolases. *Endocrinol.* 30: 265. 1942.
22. Cantarow, A., K. E. Paschkis, A. E. Rakoff and L. P. Hansen: Studies on inactivation of estradiol by the liver. *Endocrinol.* 33: 309. 1943.
23. Greep, R., H. L. Fevold and F. L. Hisaw: Effects of two hypophyseal gonadotropic hormones on the reproductive system of the male rat. *Anat. Rec.* 65: 261. 1936.
24. Fevold, H. L.: The follicle stimulating and luteinizing hormones of the anterior pituitary. Chap. *XVII*, p. 966. Sex and Internal Secretions. Williams and Wilkins, Baltimore, 1939.
25. Astwood, E. B.: The regulation of corpus luteum function by hypophysial luteotrophin. *Endocrinol.* 28: 309. 1941.
26. Reichstein, T., and C. W. Shoppee: Vitamins and Hormones. Vol. 1, pp. 345–413. Academic Press, Inc., New York, 1943.
27. Thorn, G. W., and H. Eisenburg: Studies on desoxycorticosterone. A synthetic adrenal cortical hormone. *Endocrinol.* 25: 39. 1939.
28. Tepperman, J., F. L. Engel and C. N. H. Long: A review of adrenal cortical hypertrophy. *Endocrinol.* 32: 373. 1943.
29. Selye, H.: A syndrome produced by diverse nocuous agents. *Nature* 138: 32. 1936.
30. Hertz, S., and A. Roberts: Radioactive iodine as an indicator in thyroid physiology. *III.* Iodine collection as a criterion of thyroid function in rabbits injected with thyrotropic hormone. *Endocrinol.* 29: 82. 1941.
31. Leblond, C. P.: Behavior of radio-iodine in resting and stimulated thyroids. *Anat. Rec.* 88: 285. 1944.
32. Perlman, I., I. L. Chaikoff and M. E. Morton: Radioactive iodine as an indicator of the metabolism of iodine. I. The turnover of iodine in the tissues of the normal animal, with particular reference to the thyroid. *J. Biol. Chem.* 139: 433. 1941.
33. Mackenzie, C. G., and J. B. Mackenzie: Effect of sulfonamides and thioureas on the thyroid gland and basal metabolism. *Endocrinol.* 32: 185. 1943.
34. Astwood, E. B., J. Sullivan, A. Bissell and R. Tyslowitz: Action of certain sulfonamides and of thiourea upon the function of the thyroid gland of the rat. *Endocrinol.* 32: 210. 1943.
35. Astwood, E. B.: The chemical nature of compounds which inhibit the function of the thyroid gland. *J. Pharmacol. & Exper. Therap.* 78: 7. 1943.
36. Astwood, E. B., and A. Bissell: Effect of thiouracil on the iodine content of the thyroid gland. *Endocrinol.* 34: 282. 1944.
37. Schnacher, H., A. L. Franklin and I. L. Chaikoff: On the in vitro accumulation of inorganic iodine by surviving thyroid tissue with radioactive iodine as indicator. *Endocrinol.* 34: 159. 1944.
38. Rawson, R. W., J. F. Tannheimer and W. Peacock: The uptake of radioactive iodine by the thyroids of rats made goiterous by potassium thiocyanate and by thiouracil. *Endocrinol.* 34: 245. 1944.
39. Dempsey, E. W., and E. B. Astwood: Determination of the rate of thyroid hormone secretion at various environmental temperatures. *Endocrinol.* 32: 509. 1943.
40. Mixner, J. P., E. P. Reineke and C. W. Turner: Effect of thiouracil and thiourea on the thyroid gland of the chick. *Endocrinol.* 34: 168. 1944.
41. Franklin, A. L., S. R. Lerner and I. L. Chaikoff: The effect of thiouracil on the formation of thyroxine and diiodotyrosine by the thyroid gland of the rat with radioactive iodine as indicator. *Endocrinol.* 34: 265. 1944.
42. Dempsey, E. W.: Fluorescent and histochemical reactions in the rat thyroid gland at different states of physiological activity. *Endocrinol.* 34: 27. 1944.
43. Dunn, S. J., H. L. Sheehan and N. G. B. McLetchie: Necrosis of islets of Langerhans produced experimentally. *Lancet.* 1: 484. 1943.
44. Goldner, M. G., and G. Gomori: Alloxan diabetes in the dog. *Endocrinol.* 33: 297. 1943.

45. YOUNG, F. G.: The identity and mechanism of action of the glycotropic (anti-insulin) substance of the anterior pituitary gland. *Biochem. J.* 32: 1521. 1938.
46. BENNETT, H. S.: The life history and secretion of the cells of the adrenal cortex of the cat. *Am. J. Anat.* 67: 151. 1940.
47. POLLOCK, W. F.: Histochemical studies of the interstital cells of the testis. *Anat. Rec.* 84: 23. 1942.
48. DEMPSEY, E. W., AND D. L. BASSETT: Observations on the fluorescence, birefringence and histochemistry of the rat ovary during the reproductive cycle. *Endocrinol.* 33: 384. 1943.
49. WISLOCKI, G. W., AND H. S. BENNETT: The histology and cytology of the human and monkey placenta, with special reference to the trophoblast. *Am. J. Anat.* 73: 335. 1943.
50. LEULIER, A., AND L. REVOL: Sur le cholestérol des surrénales: detection histochemique et dosages chimiques. *Bull. d'Histol. app.* 7: 241. 1930.
51. BENNETT, H. S.: Cytological manifestations of secretion in the adrenal medulla. *Am. J. Anat.* 69: 333. 1941.
52. LISON, L.: Histochemie Animale. Gauthier-Villars, Paris, 1936.
53. TURCHINI, J.: L'historadiographie-Applications. *Bull. d'Histol. app.* 14: 17. 1937.
54. RIDEAL, E. K., AND J. H. SCHULMAN: Reactions with monolayers and their biological analogies. *Nature.* 144: 100. 1939.

Abstracts of
CURRENT ENDOCRINE LITERATURE

Editor: D. A. McGINTY. *Collaborators:* ISRAEL BRAM, RUCKER CLEVELAND, JOHN W. EVERETT, ANNE FORBES, ROBERT B. GREENBLATT, E. C. HAMBLEN, CHARLES W. HOOKER, R. G. HOSKINS, THOMAS H. MCGAVACK, A. E. MEYER, DORIS PHELPS, J. P. PRATT, E. D. REIFENSTEIN, JR., PATRICIA H. SMITH, RUTH ST. JOHN, CHARLES W. TURNER, AND HAROLD WOOSTER.

BOOK REVIEW

GREENBLATT, ROBERT B.

Office Endocrinology, Second Edition. Charles C Thomas, Springfield and Baltimore, 1944, pp. 243.

This book is refreshingly different from the common run of volumes on clinical endocrinology. It comprises a compilation of graduate-grade lectures on topics frankly selected as most meaningful for the busy practitioner. The book makes no pretense to exhaustiveness and pointedly refrains from heavy discourse on the pros and cons of undetermined issues. On the other hand it attempts to deal with as many as possible of the endocrine questions that arise in the everyday practice of clinical medicine. However, the author does now and again glance back over his shoulder at his specialist colleagues and include a passing bit of technical discourse that would be difficult of comprehension to the readers to whom the book is primarily addressed.

The first section of the book deals with "female endocrinology"—chief disorders, diagnosis, and treatment—with special attention to clinical procedures, preparations and dosages. The author is not squeamish about using trade names on occasion. The exposition of his favorable experiences with androgen therapy in women is especially interesting. A second section on "hormonology" discusses in more systematic fashion the various hormone preparations and synthetics that are currently available. In a final brief section on "male endocrinology" a few of the most common endocrine disturbances are discussed. The various chapters end with well selected bibliographies.

Had the word not come to be so distressingly equated with "superficial" the book could best be characterized as "practical." It is, however, the sophisticated product of a man who, through eager experience in both the laboratory and the clinic, has seen well below the surface and has thoughtfully codified what he has learned.

The text for the most part flows easily and gains a touch of spritliness by occasional pat citations from classical lore. One interesting citation is from the author himself—an editorial that was lifted verbatim from this Journal to afford a chapter for the book. An occasional lapse from elegance of diction is noted—for example, "chronic dosage" and "women may be alleviated." The punctuation is at times somewhat impressionistic, also. The format is pleasing and the illustrations are clear and well selected.

In a book in which the empirical element bulks so large, scope for disagreement upon the part of other specialists necessarily exists but for what it frankly is, a digest of one man's experience, it offers much that is to be commended. So useful a book will no doubt progress to further editions. —*R.G.H.*

ADRENALS

BERNHARD, W. G., AND A. C. JORDAN

Bilateral adrenal hemorrhage (Waterhouse-Friedrichsen syndrome) associated with meningococcal septicemia. *J. Lab. & Clin. Med.*, 29: 357. 1944.

Of 182 cases of meningococcal septicemia observed by the authors, six were fatal. All of the six were autopsied and four proved to have the Waterhouse-Friderichsen syndrome. From each of two, the meningococcus was isolated, while no organism was obtained from blood or spinal-fluid culture in either of the others.—*T.H.McG.*

CAHILL, G. F.

The hormonal tumors of the adrenal gland. *Pennsylvania Med. J.*, 47: 655. 1944.

This is a valuable discourse on the subject, with 9 illustrative case histories. The author's summary with respect to cortical hormonal tu-

mors is as follows: 1. The hormonal syndromes may be due to an excess of androgens or estrogens or other metabolic hormones of the cortex. 2. The syndromes are determined by the type and amount of hormone or hormones produced and by the age and sex of the patient. 3. The status of the adrenals may be adequately determined by air insufflation x-ray films. 4. Removal of the tumor, if adenoma, will cure the syndrome, but often fixed changes will persist. If the tumor is carcinomatous, its removal may temporarily improve the patient. 5. Acute adrenal deficiency occurs usually in those with symptoms of Cushing's syndrome, and the treatment is that of acute deficiency in Addison's disease. The author's summarizing comments on medullary hormonal tumors are as follows: 1. The hormonal syndromes are due to an excess of epinephrine. 2. The cases vary only in degree with the amount of the hormone produced. 3. The diagnosis is made upon: (a) a typical syndrome and response; (b) on demonstration of a pressor substance; and (c) on the presence of a tumor by air insufflation x-ray films. 4. The danger period is during the operation, although at times acute adrenal deficiency may develop from the removal of cortical tissue. 5. If patients survive the operative period, the prognosis is good, because most of the tumors are benign.—*I.B.*

CLEGHORN, R. A., A. P. W. CLARKE AND W. F. GREENWOOD.

Activity of desoxycorticosterone acetate in propylene glycol by oral and intravenous routes in adrenalectomized dogs, and its effect on the cardiac arhythmia of adrenal insufficiency. *Endocrinol.*, 32: 170. 1943.

Desoxycorticosterone acetate dissolved in propylene glycol, administered orally, did not effectively maintain adrenalectomized dogs. Evidence that some absorption of the active material took place is suggested by the failure of severe adrenal insufficiency to develop before the end of 10 days' treatment. Desoxycorticosterone acetate administered to 3 dogs in severe adrenal insufficiency restored two. In these 2, the intravenous administration of desoxycorticosterone acetate in propylene glycol was followed by restoration of normal cardiac rhythm and by improvement in the general condition of the animals within about 3 hours. The opinion formerly advanced that desoxycorticosterone acetate lacks some factor necessary for cardiac metabolism is not substantiated by these later experiments.—*Author's Summary.*

FRAENKEL-CONRAT, H., M. E. SIMPSON, AND H. M. EVANS

Influence of adrenalectomy and of adrenocortical steroids on liver arginase. *J. Biol. Chem.*, 147: 99. 1943.

Adrenalectomy caused a conspicuous decrease in the arginase activity of rats' livers, exceeding that following hypophysectomy. Administration of corticosterone, 11-dehydrocorticosterone, and 11-dehydro-17-hydroxycorticosterone produced increases in liver arginase in normal, hypophysectomized, and adrenalectomized rats. Desoxycosterone at similar dose levels had no effect or slightly decreased the activity of liver arginase. No significant effects were produced by sex hormones in similar doses. The possibility exists that the effect of the adrenal cortical hormones on certain enzyme systems may be basically responsible for the role of this gland in carbohydrate and protein metabolism.—*C.W.H.*

HOFFMAN, M. M., V. E. KAZMIN AND J. S. L. BROWNE.

The excretion of pregnandiol following the administration of desoxycorticosterone acetate to rabbits. *J. Biol. Chem.*, 147: 259. 1943.

Desoxycorticosterone acetate dissolved in oil was injected subcutaneously in amounts ranging from 225 to 930 mgms. over a period of 1 to 10 days to each of eight adult rabbits. The urine collected during the injection period and for the succeeding 3 days was extracted daily with butanol. In each instance sodium pregnandiol glucuronide was identified in the combined butanol extracts. From 5.6 to 14.6 per cent of the injected desoxycorticosterone was excreted as pregnandiol, an extent of interconversion of the same order as that of the conversion of progesterone to pregnandiol in the rabbit. It is suggested that pregnandiol of adrenal origin may arise from desoxycorticosterone as well as from progesterone.—*C.W.H.*

RALEIGH, G. W., AND H. F. PHILIPBORN, JR.

Addison's disease with partial absence of adrenal cortex and gynecomastia. *Arch. Path.*, 37: 213. 1944.

A case report describes the course of Addison's disease in a 36-year-old male in whon unilateral gynecomastia had developed after 2 years of maintenance therapy with salt and desoxycorticosterone acetate. The man died at the age of 40 in Addisonian crisis precipitated by atypical

pneumonia, the etiologic agent of which was unknown. Necropsy revealed almost complete absence of the adrenal cortex and hyperplasia of the right breast.—*R.C.*

REMINGTON, J. W.

Effect of adrenal cortical extract and certain steroid hormones on the response of adrenalectomized rats to intraperitoneal injections of an isotonic glucose solution. *Endocrinol.*, 32: 129. 1943.

The ability of desoxycorticosterone acetate to protect the adrenalectomized rat against the fatal collapse which follows an intraperitoneal injection of an isotonic glucose solution has been compared with that of whole adrenal cortical extract and the sex hormones progesterone, testosterone and estradiol. The decreased ability of the adrenalectomized rat to transfer water and electrolyte from the interstitial spaces into the peritoneal cavity, via the blood stream, could not be corrected to that of the intact rat by any therapy used. Likewise the initial hemoconcentration in the period of rapid water transfer to the peritoneal cavity could not be reduced to that characteristic of the intact rat. In its ability to allow a later hemodilution, to restore urine flow, and to prevent the symptoms of fatal collapse, desoxycorticosterone acetate proved about 9 times weaker than cortical extract. As judged by the criteria employed in this experiment, there was no evidence that the action of desoxycorticosterone acetate was qualitatively different from that of cortical extract.—*Author's Summary.*

ENDOCRINE GENERAL

GITLOW, S., AND D. M. KURSCHNER

Estroben, diabetes and the menopause. *Arch. Int. Med.*, 72: 250. 1943.

Experience with diethylstilbestrol given by mouth was limited because of the recent introduction of this substance, but if one judges from the scanty available data its effect on hyperglycemia does not parallel its effect on menopausal symptoms.

This work with a limited number of subjects rather indicates that the proper patients for this treatment are those in whom diabetes develops at about the same time as the menopause, or those with aggravation of diabetes at this period. Careful work at various clinics will clarify this question.—*Courtesy Diabetes Abstracts.*

LAUBER, F. U., AND M. R. MATTICE

Microdetermination of blood glucose. *J. Lab. & Clin. Med.*, 29: 113. 1944.

This micromethod for the determination of glucose in small amounts of blood (0.1 cc.) was evolved as a "combination of parts of well-known procedures" to meet the requirements of the authors for accuracy and simplicity in the handling of quantities of blood as small as 0.1 cc. Protein is removed by Somogyi's technique, using an alkaline zinc solution. The copper-reducing substance in the filtrate was estimated by the photoelectric colorimeter after the development of the Folin-Wu blue color. The accuracy of the method has been checked by duplicate determinations in capillary and venous blood samples, by simultaneous fermentation experiments, and by the macromethods from which derived. Deviations not exceeding values from minus 1 to plus 3 mgm. per cent have been observed as a result of these comparisons.—*T.H.McG.*

LYON, R. A.

Relief of essential dysmenorrhea with ethinyl estradiol. *Surg. Gyn. & Obst.* 77: 657. 1943.

Accepting basal body temperature as an indicator of ovulatory menstrual cycles, and association of dysmenorrhea with only ovulatory cycles, 138 dysmenorrheic cycles were followed. Of these, 44 cycles were treated for 21 to 24 days, by the oral administration of 0.05 mgm. of ethinyl estradiol. Inhibition of ovulation, as indicated by basal body temperature, was associated with freedom from dysmenorrhea. After treatment of 1 or 2 cycles, the treatment was omitted. The succeeding cycle gave evidence of ovulation and the cramps recurred. There was no evidence of toxicity. The procedure is presented as a contribution to the understanding of the mechanism of dysmenorrhea and not advocated as a routine treatment.—*J.P.P.*

PASCHKIS, K. E., AND A. H. PRICE

The chloride excretion test (Cutler-Wilder-Power test) in asthenia. *J. Clin. Invest.*, 23: 29. 1944.

Fifty patients were subjected to oral glucose-tolerance tests and to the chloride excretion procedure of Cutler, Power, and Wilder. These were divided into 2 groups entirely on the basis of the subjective symptom of asthenia, of which 27 complained. Of these 27, 11 showed a Cl concentration during the 4-hour period of the third day of more than 125 mgm. per cent (the upper

limit of normal set by the original workers), and 3 a concentration exceeding 225 mgm. per cent; while in the 23 patients "not definitely complaining of asthenia, but resembling the asthenia cases in some respects, only three had a concentration of more than 125 mgm. per cent." Nine of the 17 patients showing a flat glucose-tolerance curve belonged to the asthenic group. Low blood pressure (systolic pressure below 120 mm. Hg) was found in 21 patients, of whom 15 were in the asthenic group. However, only 6 patients had a systolic pressure below 100 and a diastolic pressure below 60. One of 2 patients presenting an orthostatic hypotension was in the asthenic group. A wide variation in chloride-retaining power was noted in patients who were subjected to the Cutler-Wilder-Power procedure on 2 or more occasions. This sharply contrasted with the relatively constant results obtained in 5 healthy controls. A diagnosis of psychoneurosis was made in 38 of the 50 subjects. The authors concluded that patients suffering from asthenia may temporarily show signs of exhaustion and adrenal cortex insufficiency. They did not wish, however, to look upon the temporarily noted disturbance as indicative of Addison's disease.—*T.H.McG.*

SELYE, H.

Role of bile in absorption of steroids. *Endocrinol.*, 32: 279. 1943.

Experiments in the female rat indicate that bile plays no important role in the absorption from the intestinal tract of steroid hormones. Following oral administration of desoxycorticosterone acetate, progesterone and testosterone a high concentration of these hormones is achieved in the blood so that general anesthesia ensues. This effect is not influenced by complete transection of the common bile duct.—*Author's Summary.*

SELYE, H., O SYLVESTER, C. E. HALL AND C. P. LEBLOND

Hormonal production of arthritis. *J.A.M.A.* 124: 201. 1944.

The author reports further experiments on the previously described rheumatic fever-like syndrome produced in rats by intoxication with desoxycorticosterone acetate. The animals are sensitized to the action of DOCA by a high salt intake and the ablation of one kidney. Such animals usually develop periarteritis nodosa, nephrosclerosis and lesions in the heart and blood vessels resembling those of rheumatic fever in humans. Joint changes, however, are only infrequently encountered. If, in addition to one kidney, either the thyroid or the adrenals are removed or if the animals are exposed to cold, a high incidence of acute and chronic arthritis is obtained. Photomicrographs of the lesions are shown. The suggestion is made that rheumatic and hypertensive disease in man may be due to overproduction of adrenal cortical hormones in the "alarm reaction" which follows exposure to damaging agents. Thyroid and adrenal deficiency may favor localization of the injury to the joints by their effect on thermoregulation. There follows a brief review of the literature on the occurrence of arthritis in human endocrinopathies.—*A.P.F.*

SEVRINGHAUS, ELMER L.

Diagnostic and therapeutic problems of obesity. *J. Mich. M. Soc.*, 42: 530. 1943.

Obesity is always caused by disproportion between the intake and the expenditure of calories. Increased intake may be voluntary and conscious or not recognized because of several features. Sometimes there is excessive hunger due to hypoglycemia, habitual overfilling of the stomach, addiction to concentrated foods, or social pressures for eating. Decreased expenditure of calo-hypothyroidism, psychological or economic handicaps at activity. There are certainly constitutional and genetic types of obesity. It seems impossible to make any direct correlation with endocrine factors in the direct etiology, however.

Reducing is a very simple matter, the details of which are to be found in most of the books on diet therapy. The 1,200-calorie menu outlined has about 125 grams of carbohydrates per day. The 930-calorie menu has about 90 grams of carbohydrates per day. Both of these are prescribed in terms of simple household portions.—*Courtesy Diabetes Abstracts.*

SUGGS, W. D.

Sterility in the female. *South M. J.* 36: 616. 1943.

This paper is an analysis of the case histories of 116 barren patients. A standard plan of investigation of both partners was followed. This included a simple examination of the sperm, determination of the patency of the Fallopian tubes, and basal metabolism studies. Endocrine therapy was guided by endometrial biopsy. The basal metabolic rates of 82% of the females was below 0. Treatment included endocrine therapy, suspension of uterus, salpingoplasy, myomectomy,

oophorocystectomy, dilatation and curettage, use of the stem pessary, irradiation of pituitary and ovaries, artificial insemination with the husband's sperm, thyroid extract, wheat germ oil, and multiple vitamins. Thirty-seven pregnancies ensued, with the production of 37 living infants. There were no abortions or fetal abnormalities.—*H.A.W.*

URANGA, G.

The syndrome of estrogenic insufficiency and its treatment with blood transfusions and short waves. *Rev. Cubana obstetricia ginecol.* 6: 5. 1944.

With the purpose of supplying the total hormones in circulation transfusion is performed, women of absolutely regular cycle serving as donors. Blood (300 cc.) is taken during the first half of the cycle, mixed with 25 cc. of 10% sodium citrate solution and injected intravenously into the patient who should be in the same stage of the cycle, provided a noticeable cycle exists. During the second half of the cycle the patient receives in addition 5 to 10 mg. of Proluton. The treatment is supported by short wave treatment of the pelvis and high vitamin and iron medication, and prolonged until response is obtained. The various conditions treated comprise: primary and secondary infantilism, dysmenorrhea leucorrhea, dysparaunia, natural and artificial menopause. The various symptoms are enumerated and complete subsidence is claimed in a large number of cases.—*A.E.M.*

WAGNER, RICHARD

Endocrine and pseudoendocrine problems in childhood. *New England J. Med.*, 229: 20: 737. 1943.

Many anomalies and disturbances of growth and development and certain cases of retarded sexual development, of an abnormal accumulation and distribution of fat, of dwarfism and even of mental retardation are often mistakenly grouped as the expression of an endocrine imbalance. There are three large groups of diseases and anomalies that have certain features in common but that differ from each other by their etiology as well as by the dominance of certain characteristics. These characteristics determine the conditions in question and classify it under the heading of one of three groups: Group 1. True endocrine disorders caused by a pathologic process or anomaly of an endocrine gland; Group 2. Accentuations of physiologic phases of development, which sometimes imitate true endocrinopathies. Constitutional and familial factors are frequently involved. Transitory states, such as transitory infantilism, certain forms of obesity and disharmonic development, are included; Group 3. Congenital anomalies and multiple deviations, retardation of development, somatic as well as mental, sometimes mistaken for endocrinopathies and showing some of their essential features. Not infrequently they overlap. This group should properly be called genopathies rather than endocrinopathies. Several case histories are presented to demonstrate how complex are the endocrine problems in childhood. Group 1 is illustrated by two examples, one of congenital cretinism and another of pituitary dwarfism. Group 2 is illustrated by such examples as pseudo-Frolich syndrome, cases of retarded sexual development and also an example of disharmonic sexual development. The author concludes one should beware of becoming a victim of self-deception as a result of applying treatments that are not exact scientific achievements. The significance of many laboratory tests, such as the glucose-tolerance test and determination of the basal metabolic rate, is often overemphasized. Clinical evaluation, including body measurements, is still the most important part of the study in any given case. The fact that the term "endocrine imbalance" is used loosely and frequently is an indication that the problem is not clearly understood.—*R.B.G.*

GONADS

BARNES, JOSEPHINE

Dienoestrol for menopausal symptoms. *Brit. Med. J.*, 1: 79 (Jan. 15) 1944.

A total of 13 patients received treatment with Dienoestrol for menopausal flushing or senile vaginitis. One-tenth mg. was administered by mouth twice daily for one or more periods of 4 weeks. The results of treatment were considered good in all except a few cases. None of the patients experienced nausea or vomiting. The results obtained in this small group indicate that Dienoesterol is a safe and nontoxic estrogen. Although in a few patients better results were obtained with stilbestrol, nevertheless it has been shown that this compound when given by mouth is a potent estrogenic substance and inhibition of lactation could be obtained with one-tenth of the dosage required in the cases of stilbestrol and hexestrol. The chemical formula of Dienoestrol shows that it belongs to the hydroxyphenylhexadiene group.—*R.B.G.*

BISKIND, M. S., AND G. R. BISKIND

Inactivation of testosterone propionate in the liver during vitamin B complex deficiency. Alteration of the estrogen-androgen equilibrium. *Endocrinol.* 32: 97. 1943.

Vitamin B-complex deficiency does not significantly impair the inactivation of testosterone propionate in the liver of the male rat. This is in contrast to the results previously obtained with estrogens, the inactivation of which is strikingly impaired in vitamin B deficiency. Together with an absolute rise in the level of body estrogen which thus results, a serious alteration must occur in the estrogen-androgen equilibrium. Possible clinical consequences of these disturbances are discussed.—*Author's Summary.*

BOWLER, JOHN P. AND SCOTT F. PEDLEY

Androgen control in carcinoma of the prostate. *New England J. Med.* 230: 17: 501. 1944.

This paper presents a brief report of the earlier results of castration in 22 cases of carcinoma of the prostate seen in 1942. In every case of this series a surgical castration was done—at times in conjunction with radiation and administration of estrogen in cases in a hopelessly advanced stage. All cases in the series were those of adenocarcinoma of the prostate gland, proved either by demonstrable metastatic bone lesions by by pathological examination of removed tissue. Bone metastasis was demonstrable by x-ray examination in 10 cases, but in only 6 of these was pain given as a symptom. The serum acid phosphatase level was significantly elevated in 14 cases. One of the highest of these levels occurred in a 64-year-old patient. The case history follows.

When first seen he was completely disabled, and was admitted by ambulance, with extensive local and bony involvement and enlarged left supraclavicular nodes that were positive on biopsy. This was one of the most extreme cases encountered. All possible means of therapy were used. A transurethral resection was done because of marked obstruction, deep x-ray therapy was indicated, stilbestrol was given, and an orchidectomy was done. The preoperative x-ray film showed extensive osteoblastic metastases throughout the pelvis. Films taken three months after the orchidectomy showed extreme sclerosing of these areas, which was particularly obvious in the right ilium. By that time there was a 75 per cent recession in the supraclavicular nodes, and the general clinical result was dramatic. This improvement continued for seven months and the patient returned to overseeing his farm. At the end of eight months of normal health, extension and pain recurred, and a rapid progression to a general carcinomatosis followed. This late failure was in contradiction to what was to be expected from the initial clinical picture.

In general the authors were impressed with the promptness and completeness of symptomatic relief in these cases. The relief and comfort of 4 different cases of remission following x-ray therapy have also been striking. Furthermore, many carcinomas of the prostate are low-grade and many patients with such tumors live to a great age. It is much too early to observe the effectiveness of castration and the administration of estrogens along with the use of radiation therapy.

BROWN, R. L.

Sperm fluctuations in health and disease. *South. M. J.* 36: 619. 1943.

This paper reports the results of 4000 determinations on 447 ejaculates from 44 donors. Weekly ejaculates from one subject were studied for 2 years. Common febrile states were found to decrease the resistance of spermatazoa to spermicides as well as to normal ageing processes. Ulcerous membranous stomatitis in this subject caused a transient aspermia, followed by devitalized and morphlogically abnormal spermatozoa. Sexual excess decreased the volume of semen and number of spermatozoa, although spermicidal and ageing times remained at a fertilizing level.—*H.A.W.*

CROSSEN, R. J., AND L. LOEB

Effect of long-continued administration of an estrogen on the sex organs of mice which have passed the reproduction period. *Arch. Path.*, 37: 202. 1944.

Female mice of the CBA and C_{57} strains, 16–24 months old, were subjected to weekly injections of 100 and 200 rat units of estradiol benzoate for periods of 2.5 to 7.75 months. The 25 control mice and those of CBA stain ranged in age from 15–31 months. The various types of growth processes observed in the mammary gland, vagina, cervix and uterus were classified as *a*) intensified normal, *b*) abnormal growth processes, *c*) precancerous and *d*) cancerous changes. Chronic mechanical stimuli and long standing inflammatory changes due to infection may have helped to intensify these changes. Regeneration after acute processes had no effect on growths. The growth of tissues responsive to estrogen may be inhibited

or modified during the course of administration by factors which develop. Cancerous changes were observed in 4 of 13 mice; precancerous changes in 3. These changes were more pronounced in rats receiving 200 R.U. of estradiol benzoate than in those receiving 100 R.U. The pathologic changes in the ovaries, uteri, mammary glands and vaginae are given.—*R.C.*

EVERETT, J. W.

Further studies on the relationship of progesterone to ovulation and luteinization in the persistent-estrous rat. *Endocrinol.*, 32: 285. 1943.

Persistent estrus in the DA strain of rats was interrupted at will by a single injection of 0.5 to 1 mg. of progesterone, usually causing atresia of the large follicles and the appearance of a diestrous smear, lasting 2 or 3 days as new follicles were growing. A second injection was given on specific days of this diestrus or of the following estrous period. The effectiveness of such treatment in producing corpus luteum formation was slight in early diestrus, rose to a maximum on the 1st day of estrus (stages I or II) and then declined gradually to a negligible value when estrus had persisted longer than 8 days. The evidence tends to support the work of others which has indicated that, in the normal animal, progesterone begins to be secreted in the preovulatory phase of the estrous cycle. The repair of interstitial cells in the ovary which accompanied successful corpus luteum formation indicates that progesterone at certain times may cause a (momentary?) release of pituitary luteinizing hormone, at least in this one species and under these special conditions.—*Author's Summary.*

FORBES, T. R.

Additional data on the relative absorption rates of subcutaneous pellets of various crystalline compounds in the rat. *Endocrinol.*, 32: 282. 1943.

Uniformly prepared pellets, subcutaneously implanted in 99 adult rats, required the following periods for 90 per cent absorption: hexestrol pellets, 54 days; diethylstilbestrol dipropionate, 140 days; diethylstilbestrol methyl ether, 145 days; diethylstilbestrol methyl ether acetate, 220 days; testosterone dipropionate, 272 days. Similarly prepared pellets of anhydrohydroxy-progesterone were less than 30 per cent absorbed in 300 days. —*Author's Summary.*

FRIEDMANN, ERNST

Prostigmin in the treatment of delayed period. *Brit. Med. J.*, 1: 11 (Jan. 1) 1944.

In 94.5 per cent of the cases treated for a delayed period which was not due to pregnancy, a menstrual flow was obtained. The psychological factor was ruled out by the injection of sterile water in ten cases without a subsequent menstrual flow. Prostigmin was found to be safe and there was no tendency of the drug to interfere with the course of pregnancy. The technique employed for the administration of prostigmin was 1 mgm. on three successive days, the treatment being discontinued if, after the first or second injection, a menstrual flow followed. Usually the interval between the last injection and the onset of menstruation was 72 hours. The author recommends that the treatment be reserved for patients with previous irregular or slightly irregular menstrual cycle.—*R.B.G.*

GARDNER, W. U.

Influence of sex and sex hormones on the breaking strength of bones of mice. *Endocrinol.* 32: 149. 1943.

The 'breaking strength' of the femurs of 241 mice which had received estrogens (estradiol benzoate, estradiol dipropionate, stilbestrol or estrone) or estradiol benzoate plus testosterone propionate was determined under uniform conditions. The breaking strength of the femurs of 162 untreated mice of the same stocks was also determined. The femurs of untreated mice declined in strength as the mice advanced in age. The bones of the females were stronger than those of the males. The most radio-opaque femurs in general showed the greatest resistance to fracture. The breaking strength of the femurs was much greater in the estrogen-treated mice than in the controls of the same age groups. Estrogen-treated male mice had stronger femurs than females similarly treated. The bones of the old estrogen-treated mice were relatively stronger than those of the younger estrogen-treated mice when compared to controls of the corresponding age groups. The simultaneous injection of testosterone propionate and estrogen prevented the increased strength observed in mice given estrogens alone. The bones of female mice given testosterone propionate were much weaker than the bones of untreated controls of the same age groups. The presence of the ovaries and testes or the injected estrogenic and androgenic hormones influenced the strength of the bones of mice.—*Author's Summary.*

KAUNITZ, H., A. M. PAPPENHEIMER AND C. SCHOGOLEFF.

Protracted effect of a single dose of *dl* α-tocopheral acetate upon the testis of rats on vitamin E-deficient diet. *Am. J. Path.*, 20: 247. 1944.

dl-α-Tocopherol delayed the onset of postpubertal testicular degeneration in offspring of vitamin-depleted mothers. Administration on the 15th day of life afforded a greater protection than when given on the 6th to 8th days or on the 29th to 30th day of life.—*R.C.*

LANDAUER, W., AND B. ZONDEK

Observations on structure of bone in estrogen-treated cocks and drakes. *Am. J. Path.*, 20: 179. 1944.

Estradiol benzoate was administered to a variety of cocks and drakes of various ages. Hyperossification resulted in all cases, but to varying degrees, the younger cocks responding more readily and to a greater degree than the sexually mature cocks. Skeletal age and the presence or absence of cartilage were not factors which directly influenced or regulated the occurrence of hyperossification. The degree of hyperossification also varied with the specific bone. The earliest changes were an increased vascularization of the shaft of the long bones, accompanied by a removal of the bone salts, followed by a disappearance of fat from the marrow cavity, increased multiplication of the marrow cells and vasodilation in the marrow. After large doses of estrogen the marrow underwent fibrous degeneration with focal necrosis, production of hyalin within and outside the blood vessels and eventually the formation of new endosteal bone. Thickening of the walls of small vessels occurred at the same time. The pattern of response in the various long bones corresponded closely to the known differentials of growth activity and blood supply.—*R.C.*

LEVINE, SAMUEL A., AND WILLIAM B. LIKOFF.

The therapeutic value of testosterone propionate in angina pectoris. *New England J. Med.*, 229: 21: 771. 1943.

Testosterone propionate in doses of 25 mg. three times a week was given to 18 patients with typical angina pectoris for four weeks, and to 1 patient for seven weeks. In all but 2 cases the patients received no other medication and continued the daily routine to which they had been accustomed. Of the 19 patients, 9 were hypertensive and 1 had rheumatic aortic stenosis and insufficiency. Five had had a previous coronary occlusion. Results were judged by the amount of physical activity necessary to produce an attack of angina, and the number of nitroglycerin tablets used daily. The degree of improvement was classified as marked, moderate and questionable. Five were markedly improved at the conclusion of the treatment. Two, however, reverted to their former clinical state within six to eight weeks, 1 obtained no relief from a second series of injections after fifteen months of comparative comfort, and 1 has been followed for only one month. One patient was moderately improved, 2 questionably improved, and the remaining 11 obtained no benefit. No change in the blood pressure or electrocardiogram and no toxic effects were noted. Realizing the clinical course of angina pectoris may vary a great deal spontaneously, they are unable to conclude that testosterone propionate has any beneficial effect in this disease.—*R.B.G.*

MACHT, D. I.

Further historical and experimental studies on menstrual toxin, *Am. J. Med. Sci.*, 206: 281. 1943.

In 1923 the author published the first scientifically controlled experimental data on menstrual toxin. In the present paper the author reviews the literature appearing on this subject during the past 10 years (147 references) and supplements this with further experiments of his own. He concludes: 1) Experimental data demonstrate in the blood and secretions of menstruating women the presence of a toxic substance or menotoxin, which is poisonous for plants and animals. 2) This experimental biologic demonstration explains in large measure the numerous empirical observations on "menstrual poison" in the folklore of many countries. 3) In the light of these findings, an interrelationship is apparent between menstruation and various manifestations of disease. 4) Menotoxin has been found to be closely related pharmacologically to the phenanthrene derivatives, cholesterol and oxycholesterol; and, while it is a separate toxic entity, it is probably closely allied to the female sex hormones, which are also known to be natural products of phenanthrene and related in their structure to the sterols.—*E.C.R.,Jr.*

MORRIONE, T. G.

Effect of estrogens on the testis in hepatic insufficiency. *Arch. Path.*, 37: 39. 1944.

In 26 cases of Laennec's cirrhosis the most con-

stant finding in the testis was atrophy of the germinal epithelium and decrease in tabule size. On the basis of evidence that estrogen excess is a likely causative factor in testicular atrophy and gynecomastia of patients with cirrhosis of the liver, rats were treated with carbon tetrachloride to produce liver damage and subsequently treated with estrogens. The testis was ususually susceptible to estrogen as the result of the failure of the liver to inactivate, rather than of the biliary apparatus to excrete, the injected estrogens. No evidence was found that chronic alcoholism in man is associated with testicular degeneration unless it is concurrent with severe liver damage. —*R.C.*

NESBIT, R. M., AND R. H. CUMMINGS

Prostatic carcinoma treated by orchidectomy. *J.A.M.A.* 124: 80. 1944.

Seventy-five cases of prostatic carcinoma treated by orchidectomy have been followed for 21 months or more after the operation. The same group was analyzed 15 months earlier in a preliminary report at which time five had died. Twenty more are now dead and twenty-one more have suffered recurrences. Thus although sixty-five of the seventy-five were improved for a time, the improvement appears always to be temporary. The cases are divided into two groups, those in whom the disease was early and those in whom it was advanced, at the time of operation, and have been compared with 1000 similar, untreated cases. The course and prognosis of the early cases has not been much affected but the course of the late cases was very much improved. From this the authors argue that the maximum benefit from endocrine therapy is obtained if it is withheld until the disease becomes severe.—*A.P.F.*

PAPPENHEIMER, A. M., AND C. SCHOGOLEFF

Testis in vitamin E-deficient guinea pigs. *Am. J. Path.*, 20: 239. 1944.

The authors report that the guinea pig, like the rabbit, fed an E-deficient diet, developed muscular dystrophy before changes occurred in the testis, in contrast to the rat under the same condition.—*R.C.*

PEARLMAN, W. H., AND GREGORY PINCUS

The metabolism of estrone in men. *J. Biol. Chem.*, 147: 379. 1943.

Up to 160 mgm. of estrone acetate was injected into each of seven young men. From the strong phenolic fraction of the urine collected for 96 hours after the injection, crystalline estriol was obtained. The normally extremely low estriol and total estrogen content of the urine of males plus the rapid decrease in estriol after 96 hours following the injection of estrone are taken as evidence that the estriol in this study arose from the injected estrone rather than from an endogenous estrogen. The high concentration of estrogen in the weakly acidic, phenolic, non-ketonic fraction was apparently α-estradiol as indicated by the changes in the estrogenic activity of this fraction after mild oxidative procedures.—*C.W.H.*

PINCUS, G.

New color reaction for certain urinary 17-ketosteroids. *Endocrinol.*, 32: 176. 1943.

An intense blue color (absorption maximum at 610 $\mu\mu$) is developed by androsterone and its isomers and by androstenone-17 after heating with concentrated $SbCl_3$ solution (or amorphous $SbCl_3$) and dilution with glacial acetic acid. Androsterone succinate and androsterone sulfate develop the same intense color. Androstanediol develops qualitatively the same color but in reduced intensity. Dehydroisoandrosterone and its succinate develop a weak yellowish-blue color and pregnandiol a weaker, somewhat similar color. Testosterone, allopregnanolone, epipregnanolone, androstenedione, androstanol-3β-(?)-one, progesterone, cholestenone, and cholesterol develop extremely weak yellow colors. The optimal method for development of the typical stable color requires a) using a solution containing 3.8 gm. of $SbCl_3$ per 0.9 cc. of glacial acetic acid and 0.1 cc. of acetic anhydride which is added drop by drop in 0.2 cc. to the dried steroid preparation; b) heating, with shaking for 20 minutes in a boiling waterbath; c) diluting with a solution containing 95 parts of glacial acetic acid to 5 parts of distilled water; d) incubating in the dark at room temperature for 40 to 60 minutes. When chloroform is used as the diluent, a qualitatively different color develops with androsterone, having absorption maxima at 560 and 620 $\mu\mu$. Dehydroisoandrosterone with chloroform dilution develops a similar, less intense color. Androsterone with acetic anhydride dilution develops a greenish color with absorption maxima at 460 and 610 $\mu\mu$. The application of the color reaction to urinary neutral ketonic extracts from the urines of men and women gives a color titer less than that of the Zimmerman titer, the largest difference (36 to 49 per cent less) occurring in the non-alcoholic ketonic fractions.—*Author's Summary.*

PRATT, P. C.

Evidence against a progesterone-like action of ascorbic acid. *Endocrinol.*, 32: 92. 1943.

In a series of rabbits ascorbic acid (vitamin C) was administered subcutaneously, and also locally into the uterus, in varying dosage during periods of 3 to 10 days. Contrary to a previous report no effects similar to those of progesterone were obtained.—*Author's Summary.*

PRINCE, C. L., AND S. A. VEST

Carcinoma of the prostrate. *South. M. J.* 36: 680. 1943.

This paper is a study of 189 cases of carcinoma of the prostate, 130 of which were diagnosed microscopically. The mean age of these patients on admission was 69.4 years. The chief symptoms have been frequency and difficulty of urination, nocturia and, rarely, dysuria and pain from skeletal metastases. In advanced cases diagnosis can be based on palpation of the carcinomatous gland; in earlier cases biposy is helpful. Almost all treatment has been by radical perineal prostatectomy; castration has been used in some of the later cases. The average duration of life in these patients has been 22.7 months. This should be contrasted with the normal life expectancy of 9.5 years for men of the mean age of this group. If metastases were present when the patient was first seen the average duration was 11.4 months. The authors believe that early diagnosis and radical perineal prostatectomy present the only partially certain cure for this condition.—*H.A.W.*

RICHARDS, MARION B.

The dietary factor in reproduction and lactation. *Brit. Med. J.*, 2: 418 (Oct. 2), 1943.

Experiments on rats were carried out with the view of determining the effect on reproduction in rats by supplementing a poor human dietary by additions of inorganic calcium and vitamin B_1; to test the effect of dried yeast as a source of vitamin B_1, etc. and to test the influence during the breeding period of an increased milk intake along with these supplements. The author concludes from his experiments that the diet is important in matters concerning breeding performances in animals in controlled environments and indicates what a large part diet may possibly play in the problem of infant mortality in human beings.

The experiment on animals showed that the addition of certain substances, such as inorganic calcium, milk, and dried yeast, improved breeding performances and decreased the number of deaths during the suckling period.—*R.B.G.*

SMITH, GEORGE VAN S.

Therapy with female sex hormones. *New England J. Med.*, 230: 12: 339. 1944.

The author discusses functional disorders of menstruation such as primary functional amenorrhea, secondary or acquired functional amenorrhea, dysmenorrhea and functional uterine bleeding; disorders associated with menstruation such as premenstrual tension, menstrual headaches, cyclic mammary pain, mid-month pain or bleeding. Methods for the alleviation of these conditions are given. Notes on the menopause, functional sterility, frigidity, vaginitis and kraurosis vulvae are also given.—*R.B.G.*

HYPOPHYSIS

CANTILO, ENRIQUE, AND CARLOS FERNANDEZ SPERONI

Endocrinopathies XVIII. Gigantism? *Semana medica.* 50, II: 1457. 1943.

A boy of 13 years measured 180 cm. and had a weight of 127 kg. The extremities were disproportionately long; the sexual development was retarded, the genitals corresponding in size to those of a 10 year old. Pubic hair was absent. The case is characterized by the name pregigantism. The sella turcica was normal, the epiphyseal bone development corresponded to the prematurity age. The BMR was -16%, the glucose tolerance flat but the hyperglycemic curve after adrenaline and insulin hypoglycemia were normal; cholesterol 0.175%. The treatment consisted in injections of testosterone proportionate in oil, 10 mg. twice weekly; thyroid powder 0.6 gm., adrenal cortex substance 0.1 gm. and total testicle substance 0.9 gm. twice daily; α, β, γ, tocopherol 5 mg. daily. Examination after three years showed: body weight 184.5 cm., ossification of the epiphyses, no change in glucose tolerance, BMR -9%, weight 103 kg., perfect sexual development. The question is left open whether the favorable development is a consequence of the treatment or a spontaneous adjustment.—*A.E.M.*

HELLBAUM, A. A., AND R. O. GREEP.

Qualitative changes induced in gonadotropic complex of pituitary by testosterone propionate. *Endocrinol.*, 32: 33. 1943.

Determinations were made of the relative content of follicle-stimulating (FSH) and lutein-

izing (LH) (ICSH) factors in the pituitaries and blood serum of 71 normal adult male rats, 42 castrated untreated adults and 53 castrated males which had been treated for periods of 15 to 45 days with testosterone propionate. The results indicate that the internal secretion of the testes brings about the release of the luteinizing factor from the pituitary, and suppresses the liberation of the follicle-stimulating hormone. The pituitaries of normal male rats contain primarily follicle-stimulating hormone while the blood serum of these animals contains luteinizing hormone, and small amounts of follicle-stimulating hormone. Following castration the luteinizing hormone, as well as follicle-stimulating hormone, are markedly increased in the pituitary; the follicle-stimulating hormone in the blood stream is also present in greater amounts, whereas the luteinizing hormone appears to be decreased. Treatment of castrated rats with testosterone propionate reduced the luteinizing hormone content of the pituitary, but had relatively little effect on the follicle-stimulating hormone. In the blood serum of these animals, the amount of follicle-stimulating hormone was lowered, whereas the luteinizing hormone appeared to be increased after 15 and 30 days of treatment but not after 45 days of treatment.—*Author's Summary.*

METZ, H. M., AND R. W. LACKEY

Peptic ulcer treated with the aid of posterior pituitary extract. *South. M. J.* 36. 747. 1943.

The authors have obtained satisfactory clinical results in 74% of a series of 418 unselected cases of peptic ulcer treated with the aid of posterior pituitary extract. Intranasal insufflation of desiccated posterior pituitary powder is used as a supplement to the rational medical management of patients with uncomplicated peptic ulcer. Both in humans and experimental animals the gastric hypersecretion, gastric and duodenal hypermotility and hyperemia of the gastric mucosa characteristic of this disease revert towards normal under the influence of this hormone.—*H.A.W.*

PERLOFF, W. H., E. ROSE AND F. W. SUNDERMAN

Therapeutic observations in Cushing's syndrome. Effect of various agents on calcium, phosphorus and nitrogen excretion in a patient with pituitary basophilism. *Arch. Int. Med.* 72: 494. 1943.

The case of a 30 year old woman with pituitary basophilism in whom skeletal changes were particularly striking and in whom the diagnosis was reached by exclusion is reported. Studies of the concentration of calcium, phosphorus, protein and phosphatase in the serum, the dextrose tolerance and the excretion of calcium, phosphorus and nitrogen before and after the use of various therapeutic agents and with diets of varying calcium content are reported. The therapeutic agents employed included estradiol benzoate, testosterone propionate, vitamin D_2, calcium gluconate and lactate and diethylstilbestrol, in varying combinations. Subjective and objective responses to treatment are described, and the observations are compared with those in similar studies reported by others. The possibility is mentioned that spontaneous variations in the intensity of the various metabolic aberrations in Cushing's syndrome may explain some of the discrepancies in the studies reported to date. Several possible explanations of the skeletal decalcification characteristic of the syndrome are briefly considered. It is concluded that no completely satisfactory explanation of the skeletal demineralization in Cushing's disease is yet available.—*Authors' Summary.*—*I.B.*

PLAUT, A., AND E. GALENSON

Concretions in the anterior lobe of the human embryo and the newborn. *Am. J. Path.*, 20: 223. 1944.

Concretions were present in the pituitary glands of all of 150 newborn children and infants up to the seventh postnatal month. There was no sex difference in the frequency of the occurrence of the concretions. The great majority were located in the anterior lobe, usually surrounded by epithelial cells of all 3 types. The shape of the concretions varied, more than half being ovoid, the rest round, pyramidal or irregular in outline. The authors believe the concretions to be formed under the influence of maternal hormones.—*R.C.*

SCHLEYER, E.

Anaphylactic shock after posterior pituitary extract injection. *Brit. Med. J.*, 1: 255. 1944.

An unusual and alarming reaction to pituitary extract in an unmarried woman, age 22, who was being treated for menorrhagia is reported. Within a few minutes after the injection of 1 cc of posterior lobe pituitary extract intramuscularly, the patient complained of severe pains in the head, feeling of apprehension, blurred vision. This was soon followed by swelling of the eyelids, nose and

lips and generalized erythema, as well as vomiting, etc. The patient responded to coramine injections and the symptoms completely subsided within a week. A noteworthy fact in the patient's history was that the patient had urticaria after eating fish during childhood. The author felt that the picture resembled, to a certain extent, anaphylactic shock after serum injection and advises that the use of pituitary extract be avoided in cases with a history of allergy.—*R.B.G.*

PANCREAS

BEASER. S. B., A. RUDY AND A. M. SELIGMAN.

Capillary fragility in relation to diabetes mellitus, hypertension and age. *Arch. Int. Med.* 73: 18. 1944.

In the course of investigating diabetic retinitis, many instances of increased capillary fragility were noted in the absence of blood dyscrasia or obvious vitamin C deficiency. For this reason it was considered important to investigate capillary fragility in diabetes. During the authors' investigation of methods for measuring capillary fragility, it was found that of the positive pressure methods tried on a group of diabetic patients, Wright's method yielded the most reliable results. A group of 54 adult patients (15 with hypertension) and 67 nondiabetic patients (21 with hypertension) were tested by Wright's method. The incidence of increased capillary fragility was greatest in the fifth and sixth decades. The diabetic patients showed a greater incidence of increased capillary fragility at each age decade than the nondiabetic subjects. In diabetic hypertensive patients the test showed a greater incidence of increased capillary fragility at the higher pressure levels (midway between systolic and diastolic pressure), as used by Wright, than at a lower arbitrary level (100 mm. of mercury) when performed simultaneously on the 2 arms. Without further study no conclusions can be drawn concerning the proper pressure at which the positive pressure test should be performed on hypertensive patients.—*I.B.*

BLOTNER, HARRY, ROBERT W. HYDE AND LOWELL V. KINGSLEY

Studies in diabetes mellitus and transient glycosuria in selectees and volunteers. *New England J. Med.*, 229: 24: 885. 1943.

This paper presents certain clinical and socio-economic studies on diabetes mellitus and transient glycosuria that occurred in 45,650 consecutive selectees and volunteers, aged eighteen to forty-five years, who appeared for final examination at the Boston Armed Forces Induction Station.

The incidence of glycosuria was found to be 367 cases, or 0.8 per cent of the men examined. The cases of glycosuria were divided into three groups with the number of cases as follows: 208 cases of diabetes mellitus; 126 cases of transient glycosuria and 33 cases of renal glycosuria. Of the 208 cases of diabetes, 107 were mild, 58 were moderate and 43 were severe.

The physical condition of the men with glycosuria did not differ from that of the nondiabetic men, except that mild hypertension appeared in 7.0 per cent of the diabetic men and in 5.0 per cent of those with transient glycosuria, compared with 2.2 per cent in the control group.

The inheritance of diabetes was of interest because family histories of diabetes were obtained in 32 per cent of the diabetic cases, in 9 per cent of those of transient glycosuria, as compared with 5.2 per cent of 2293 consecutive non-diabetic selectees. The number of diabetic relatives per family of each diabetic man was appreciably greater than that of the nondiabetic men.

The nationalities, as based on the birthplace of the parents of the selectees, were studied. The incidence of diabetes and transient glycosuria was lower in the American group and higher in the non-American group, as compared with the incidence of the nationalities in the control group. The incidences of diabetes in the Jews and the Irish were outstanding.—*R.B.G.*